The tandem catalytic asymmetric allene diboration/imine allylation and the asymmetric transition-metal-catalyzed conjugate allylation of activated enones

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THE TANDEM CATALYTIC ASYMMETRIC ALLENE DIBORATION/IMINE ALLYLATION AND THE ASYMMETRIC TRANSITION-METAL-CATALYZED CONJUGATE ALLYLATION OF ACTIVATE ENONES

a dissertation

by

JOSHUA DANIEL SIEBER

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ABSTRACT

JOSHUA D. SIEBER: The Tandem Catalytic Asymmetric Allene Diboration/Imine Allylation and the Asymmetric Transition-Metal-Catalyzed Conjugate Allylation of Activated Enones

(Under the direction of: Professor James P. Morken)

Described herein are methods for asymmetric allylation. Chapter 1 describes the scope of the Pd-catalyzed asymmetric diboration of prochiral allenes. The products of this process possess both a chiral allylboronate functional group and a vinylboronate moiety. The allylboronate functionality can subsequently be used for imine allylation, without isolation of the diboron intermediate, resulting in the formation of atypical allylation products through a tandem, one-pot sequence. Furthermore, enantioselection in the catalytic diboration and chirality transfer in the subsequent imine allylation are high; thus, non-racemic, protected homoallylic amines, and other derivatives, are produced in high enantiomeric excess. Chapter 2 describes the discovery and development of a transition-metal-catalyzed asymmetric conjugate allylation of allylboronate ester nucleophiles to activated enones. The scope, utility, and mechanistic aspects of this new reaction are discussed.

Dedicated to my loving family:

Richard J. Sieber
Mary E. Sieber
Tammy S. Sieber
Richard W. Sieber, D.P.M.
Rachel E. Sieber
Chumly M. M. Sieber

Also to:

Professor Stephen C. Hoops
for inspirational instruction in organic chemistry

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TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF SCHEMES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Å	angstrom
Ac_2O	acetic anhydride
AcOH	acetic acid
BBN	borabicyclo[3.3.1]nonane
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
BINOL	1,1′-binaphthalene-2,2′-diol
$(Boc)_2O$	di-*t*-butyl dicarbonate
$B_2(pin)_2$	bis(pinacolato)diboron
brsm	based on recovered starting material
n-BuLi	*n*-butyllithium
t-BuLi	*t*-butyllithium
CDI	carbonyl diimidazole
cee	conservation of enantiomeric excess
cod	1,5-cyclooctadiene
COSY	^1H-^1H correlation spectroscopy
DAK	dialkylidene ketone
dba	dibenzylideneacetone
o-DCB	1,2-dichlorobenzene
DCC	*N*,*N*-dicyclohexylcarbodiimide
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine

DMF	*N*,*N*-dimethylformamide
dppf	bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
EDCI	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
eq	equation
equiv	equivalents
EtOAc	ethyl acetate
EtOH	ethanol
GLC	gas-liquid chromatography
HPLC	high performance liquid chromatography
HSQC	heteronuclear single-quantum correlation spectroscopy
LAH	lithium aluminum hydride
MeOH	methanol
MS	molecular sieves
n/a	not applicable
NBSH	*o*-nitrobenzenesulfonylhydrazine
n.d.	not determined
$Ni(cod)_2$	bis(1,5-cyclooctadiene)nickel
NMR	nuclear magnetic resonance spectroscopy
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy

PCy_3	tricyclohexylphosphine
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
pin	pinacol
psig	pounds per square inch gauge
pyr	pyridine
RAMP	(*R*)-1-amino-2-(methoxymethyl)pyrrolidine
RBF	round-bottom flask
RCM	ring-closing metathesis
rt	room temperature
SAMP	(*S*)-1-amino-2-(methoxymethyl)pyrrolidine
SFC	supercritical fluid chromatography
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin-layer chromatography
TsOH	*p*-toluenesulfonic acid monohydrate

Chapter 1

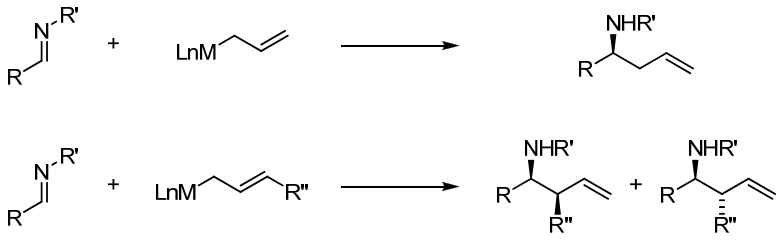
The Pd-Catalyzed Enantioselective Diboration of Allenes and its Application to the Allylation of Imines

I. Introduction

Optically active chiral amines are commonly found in natural products and commercial drugs. In addition, amine functional groups have found widespread use in chiral ligands for asymmetric transition-metal-catalyzed processes. Therefore, methods to produce chiral amines in enantiomerically enriched form are highly desirable. One of the most useful ways to create a stereogenic carbon atom with an attached nitrogen atom starting from simple prochiral starting materials is by the addition of an allylmetal reagent to an imine electrophile (Scheme 1.1).[1] This procedure affords chiral homoallylic amines, wherein facial selectivity can be dictated using substrate or reagent control. Furthermore, use of appropriately substituted allylmetal reagents simultaneously creates two new stereocenters. These methods represent powerful tools for the efficient construction of chiral amines.

[1] For recent reviews, see: (a) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815. (b) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541.

Scheme 1.1: Stereoselective Addition of Allylic Metal Reagents to Imines

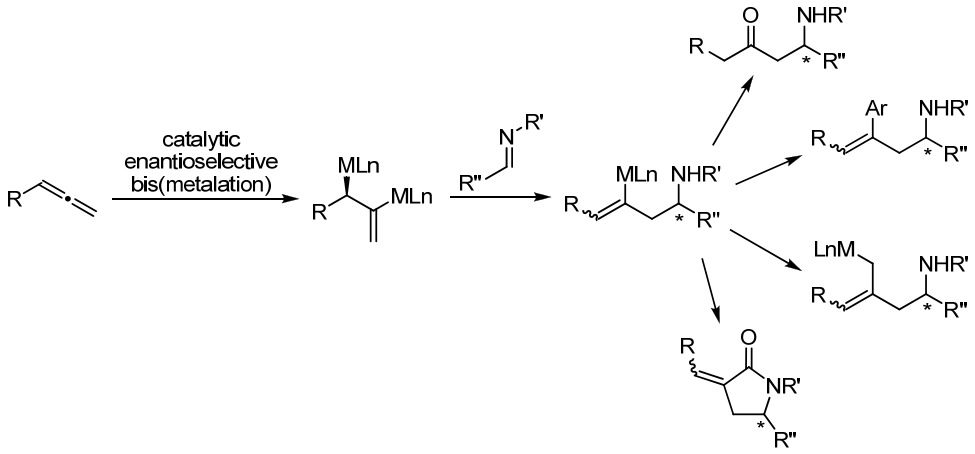


With the goal of developing synthetically-useful catalytic bis(metalations) of unsaturated carbon-carbon bonds,[2] we envisioned that a bis(metalation) of the internal olefin of an allene would provide a practical allylmetal reagent for imine allylation (Scheme 1.2). For the overall process to be synthetically valuable, the catalyst for the bis(metalation) must afford the product in high enantioselectivity, and chirality transfer in the imine addition reaction must be high. If these requirements could be met, the imine allylation product resulting from this sequence would contain a vinylic carbon-metal bond, which may be converted into a wide variety of useful organic synthons with high enantiomeric purity. To accomplish these goals, we chose to study the addition of bis(boronate) esters to allenes. The high stability of organoboronate esters makes them attractive;[2e] however, no catalytic asymmetric diboration of prochiral allenes was known prior to our work.[3]

[2] For reviews on metal catalyzed bis(metalations) of unsaturated carbon-carbon bonds, see: (a) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221. (b) Marder, T. B.; Norman, N. C. *Topics in Catalysis* **1998**, *5*, 63. (c) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392. (d) Beletskaya, I. *Chem. Rev.* **2006**, *106*, 2320. (e) Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717.

[3] (a) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328. (b) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766.

Scheme 1.2: A New Allylmetal Reagent for Imine Allylation



II. Background

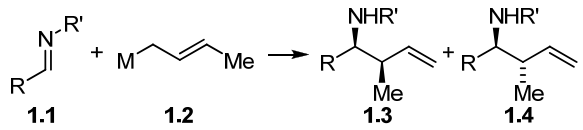
A. Diastereoselective Imine Allylation Using Substituted Allylmetals

The addition of crotylmetal reagents to imines was initially investigated by Yamamoto.[4,5] A selection of these results is shown in Table 1.1, where it can be seen that selectivity in the crotylation is highly dependent on the choice of the metal used in the reaction. When Li, Mg, or Sn reagents are employed, the *syn* diastereomer is afforded in moderate diastereoselectivities. However, the use of crotylboron reagents (entry 4) gave exclusively the *anti* product. Interestingly, in the case of boron, the nature of the imine dictates which diastereomer is formed in the reaction. For both aryl and linear-aliphatic imines bearing small substituents on nitrogen (R′ = linear and alkyl), the *syn*-product is favored in a 75:25 to 85:15 ratio. For linear-aliphatic imines where the substituent on nitrogen is branched (R′ = *i*-Pr), complete *syn* selectivity results; however, the analogous aryl imines slightly favor the *anti*-allylation product (65:35 *anti*:*syn* when

[4] Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1985**, *50*, 3115.
[5] For a review of allylmetal addition reactions, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

R = Ph). Furthermore, when branched aliphatic imines are used (R = *i*-Pr), moderate *anti* selectivity is again observed (~30:70).

Table 1.1: Crotylation of Imines



1.1 **1.2** **1.3** **1.4**

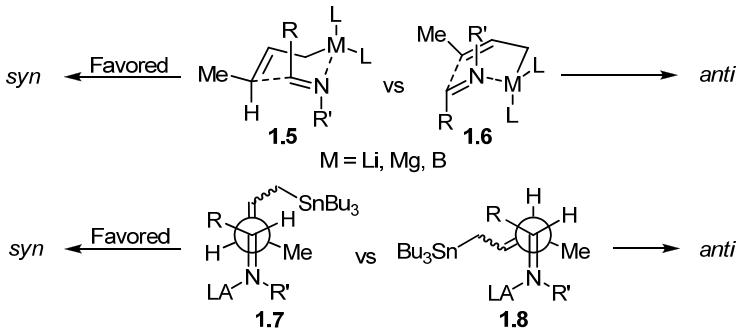
entry	R	R′	M	**1.3**:**1.4** (*syn*:*anti*)	% yield
1	Ph	Ph	Li	60:40	50
2	Ph	Ph	MgCl	74:26	95
3	Ph	Ph	9-BBN	0:100	93
4	Ph	Ph	$SnBu_3/BF_3$	75:25	80

Diastereoselectivity in these reaction can be explained by Zimmerman-Traxler[6] chair-like transition states in the cases where M = Li, Mg, or B (Scheme 1.3). Chair-like transition structure **1.5** is preferred over the boat-like transition structure **1.6**.[4,5] With allylboranes, the variation in selectivity with substrate structure is dependent more on the steric bulk of the group on nitrogen than on the size of the carbon substituent. That is to say, as the size of R′ increases, a penalizing 1,3-diaxial interaction between this group and the bridgehead proton of the 9-BBN ring destabilizes **1.5** relative to **1.6**. This phenomenon is not observed with other metals because the weaker interaction between the lone pair on nitrogen and the metal alleviates the 1,3-interaction. In the case of

[6] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

crotylstannanes, these reagents react through open transition states and addition of a Lewis acid is required for reaction. Transition structure **1.7** is responsible for formation of the *syn* product in the crotylstannylation of imines.

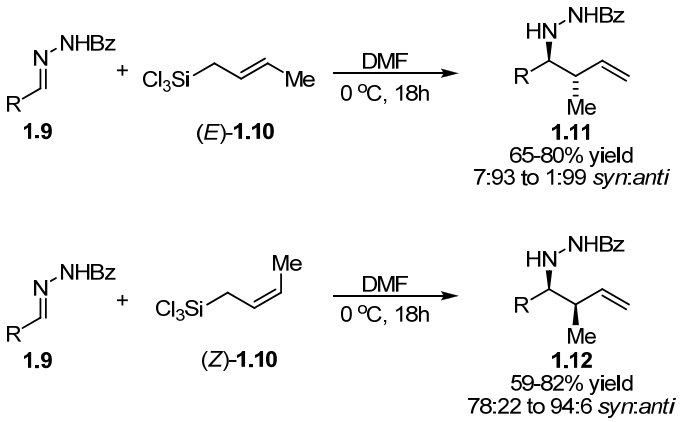
Scheme 1.3: Rational for Diastereoselectivity in the Crotylation of Imines



Kobayashi[7] has used crotylsilanes for diastereoselective crotylation of benzoylhydrazones (**1.9**, Scheme 1.4). Both aromatic and aliphatic hydrazones react under the optimized procedure with good diastereoselectivities. Importantly, the use of the *E*- or *Z*-crotylsilanes provides the *anti* or *syn* diastereomer of product, respectively. Thus, either diastereomer of product can be conveniently prepared by the correct choice of crotylsilane.

[7] Kobayashi, S.; Hirabayashi, R. *J. Am. Chem. Soc.* **1999**, *121*, 6942.

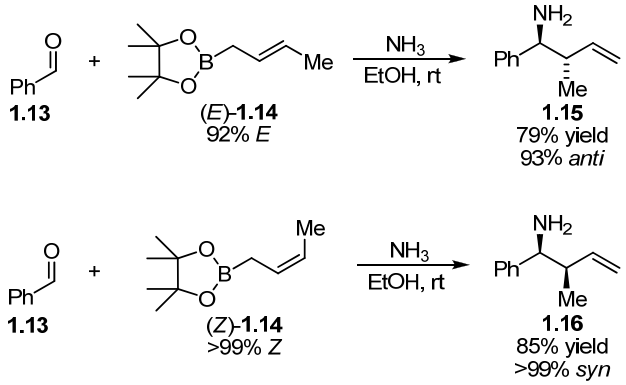
Scheme 1.4: Diastereoselective Crotylsilation



Kobayashi has developed a novel allylation where the imine is formed *in situ* from an aldehyde and an ammonia source.[8] Notably, this was done using allylboronate esters as the nucleophile in the crotylation reaction (Scheme 1.5). The use of crotylboronates (*E*)-**1.14** and (*Z*)-**1.14** affords amines **1.15** and **1.16**, respectively, in a stereospecific manner. In these cases, the ammonia derived imine (the condensation product between benzaldehyde and ammonia) is allylated in preference to benzaldehyde that may be present in solution due to the equilibrium between aldehyde and imine; thus, the homoallylic amine product is formed directly.

[8] Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182.

Scheme 1.5: Crotylboration of *in situ* Prepared Imines



B. Substrate Control for Diastereoselective Imine Allylation

The study of diastereoselective additions of organometallic reagents to α-chiral aldehydes is arguably one of the earliest contributions to the chemical literature which led to the construction of useful models for the prediction of acyclic stereocontrol.[9] Diastereocontrol in the addition of allylmetal reagents to α-chiral imines was first explored by Yamamoto.[10] As depicted in Table 1.2, imine **1.17** is allylated with a variety of allylmetal reagents in good to excellent diastereoselectivity. The Cram-addition[9a] product is the major diastereomer isolated in these reactions. Notably, the allylation of imines is generally more selective than the analogous allylation of α-chiral aldehydes.

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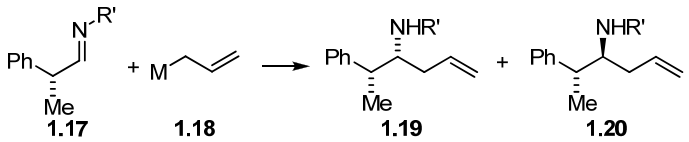
[9] (a) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367. (c) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199. (d) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (e) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162. (f) Houk, K. A.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y. –D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108. (g) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc. Chem. Commun.* **1990**, 456. (h) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc. Chem. Commun.* **1991**, 327. (i) Wu, Y. –D.; Tucker, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018. (j) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 8991. (k) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462 and references therein.

[10] (a) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031. (b) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778.

This phenomenon results from the fact that the α-stereocenter of an α-chiral imine occupies the axial position in the cyclic chair-like transition state of the allylation (Figure 1.1, **1.21** and **1.22**); the chair preference arises because of the *E*-configuration of the imine. The allylmetal reagent preferentially adds to the imine through **1.22** to avoid the penalizing steric interaction that is present between R_m and the coordination sphere of the allylmetal in transition structure **1.21**. In comparison, since the α-stereocenter of an α-chiral aldehyde occupies the equatorial position in transition structure **1.23**, steric interactions between the α-chiral stereocenter of the aldehyde and the ligands of the allylmetal are not present. Thus, lower diastereoselectivities are typically observed.[5]

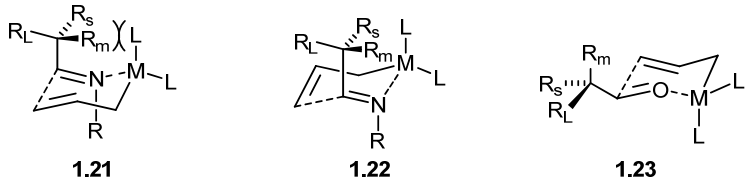
Table 1.2: Diastereoselective Addition of Allylmetals to α-Chiral Imines



1.17 **1.18** **1.19** **1.20**

entry	R′	M	**1.19**:**1.20** (Cram:anti-Cram)
1	*n*-Pr	9-BBN	96:4
2	*i*-Pr	9-BBN	100:0
3	*n*-Pr	$SnBu_3/TiCl_4$	93:7
4	*i*-Pr	$SnBu_3/TiCl_4$	92:8
5	*n*-Pr	MgCl	84:16
6	*n*-Pr	MgBr	68:32
7	*i*-Pr	MgCl	70:30

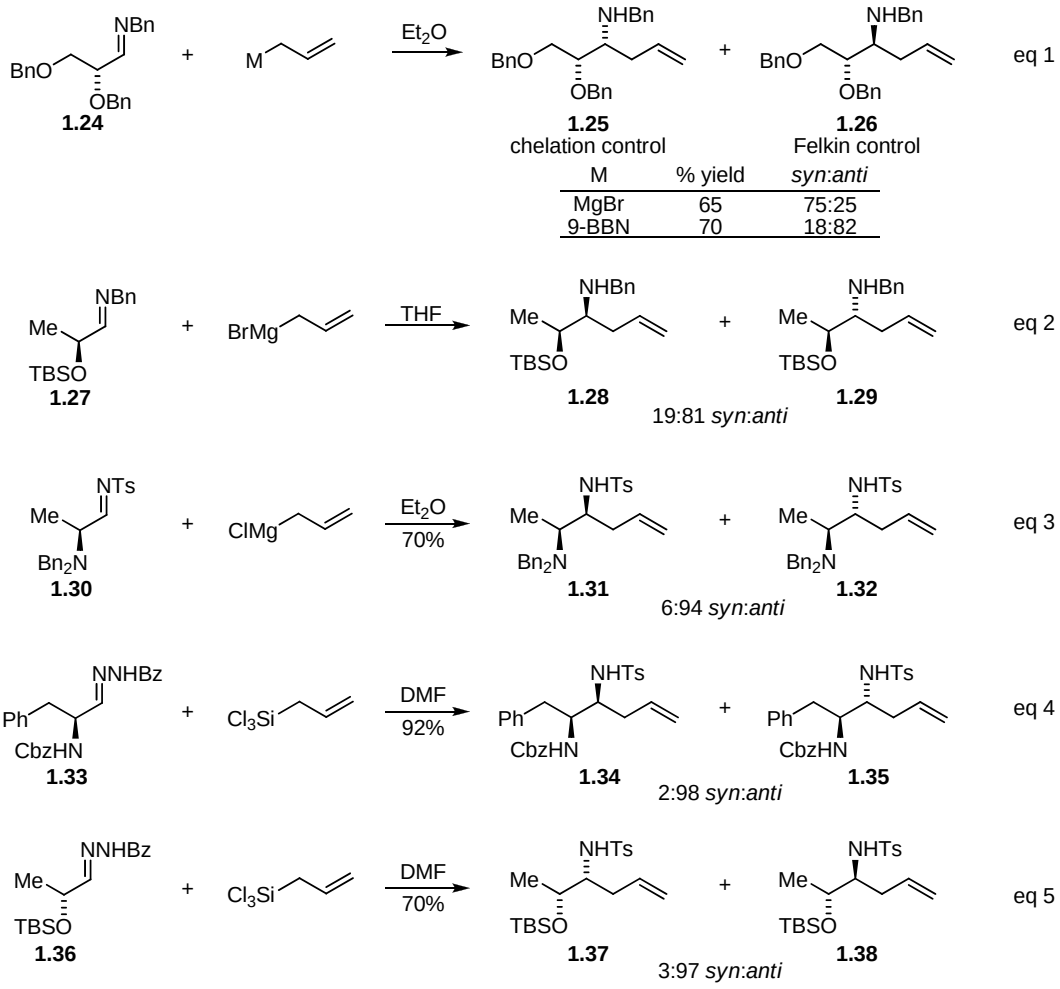
Figure 1.1: Transition State Models for Allylation of α-Chiral Imines and Aldehydes



Chiral imines bearing α-heteroatoms undergo allylation under either Felkin[9c] or chelation control, depending on the allylmetal reagent used. For example, when imine **1.24** is subjected to allylmagnesium bromide, the major *syn* product results, as predicted by chelation control (Scheme 1.6, eq 1).[11] The use of allyl-9-BBN, however, results in formation of the *anti* diastereomer, as predicted by Felkin control (the benzyl ether being the large group). Furthermore, imines **1.27**[12] and **1.30**[13] undergo Felkin-controlled allylation when allylic Grignard reagents are used (Scheme 1.6, eq 2 and 3). In addition, when hydrazones are employed as electrophiles, allylsilanes can be used as nucleophiles and excellent diastereoselectivity results (Scheme 1.6, eq 4 and 5).[14]

[11] Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Díez, R.; Galvez, J. A. *Eur. J. Org. Chem.* **2002**, 3763.
[12] Cainelli, G.; Giacomini, D.; Galletti, P.; Quintavalla, A. *Eur. J. Org. Chem.* **2002**, 3153.
[13] Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hübel, M. *Angew. Chem. Int. Ed.* **1991**, *30*, 103.
[14] Kobayashi, S.; Hirabayashi, R. *J. Am. Chem. Soc.* **1999**, *121*, 6942.

Scheme 1.6: Allylmetal Additions to α-Heteroatom α-Chiral Imines

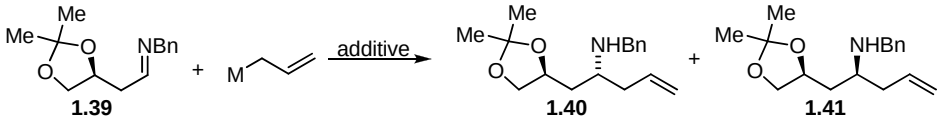


Alkoxy substitution at the β-position has also been shown to control the stereochemistry of allylmetal additions.[15] Allylation of chiral imine **1.39** with allylmagnesium chloride or allyltributylstannane gave the chelation control addition product (Scheme 1.7). When allylmagnesium chloride is used, the addition of $CeCl_3$ increases the diastereoselectivity from 67:33 to 89:11 *anti*:*syn*. Formation of the *anti*

[15] Shimizu, M.; Morita, A.; Fujisawa, T. *Chem. Lett.* **1998**, 467.

product is believed to come from external addition of the allyl nucleophile to the chelated substrate. In the case of allyllithium, the *syn* diastereomer is favored and presumably does not arise from chelation control.

Scheme 1.7: 1,3-Asymmetric Induction in the Allylation of Imines



M	additive	% yield	*anti*:*syn*
MgCl	none	62	67:33
MgCl	$CeCl_3$	54	89:11
$SnBu_3$	$AlCl_3$	54	>99:1
Li	none	46	29:71

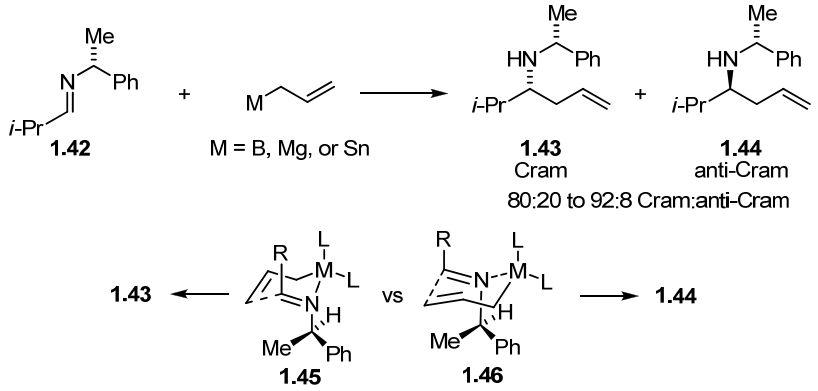
C. Diastereoselective Imine Allylation Using Chiral Auxiliaries

The use of chiral auxiliaries to control facial selectivity in the addition of allylmetals to imine electrophiles has been widely examined.[1a] For an auxiliary to be useful, a convenient installation and cleavage protocol needs to be established. For these reasons, chiral auxiliaries attached to the nitrogen atom of the imine are particularly useful and are the topic of this section. Chiral amines, including naturally occurring amino-acids, are attractive auxiliaries because they are widely available, and condensation between the amine and an aldehyde provides a convenient installation method for the auxiliary.

Seminal work in this area was conducted by Yamamoto and coworkers,[10b] who examined the allylation of imines prepared from the condensation of α-methylbenzylamine with aldehydes. When imine **1.42** is treated with allylmagnesium,

allylboron, or allylstannane nucleophiles, the Cram product **1.43** is formed in preference to anti-Cram product **1.44** (Scheme 1.8). The diastereoselectivity of the reaction can be explained through the cyclic transition structures **1.45** and **1.46**, where steric interactions between the stereocenter on the imine and the ligands are minimized by directing the hydrogen atom substituent toward the metal. The allyl group then adds to the more accessible face of the imine, away from the other substituents on the chiral center. In the case of allyltributylstannane, $TiCl_4$ is used as a Lewis acid. Good Cram selectivity in this case is rationalized by transmetalation of the allyl group from Sn to Ti, followed by allylation through **1.45** where M = Ti.

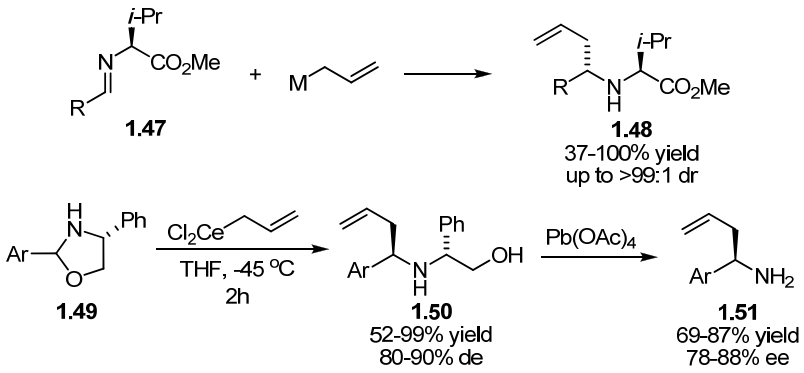
Scheme 1.8: α-Methylbenzylamine as a Chiral Auxiliary for Imine Allylation



Amino acids and vicinal aminoalcohols have been explored as chiral auxiliaries for imine allylation due to their wide availability. Methyl-(*S*)-valinate derived imines (Scheme 1.9, **1.47**) provide excellent diastereocontrol in the addition of a variety of allylmetal reagents including allylcopper, allylcerium, allylaluminum, allyllead,

allylbismuth, and allylmagnesium halides.[16] Here, the nature of the R-group on the imine affects the diastereoselectivity of the reaction. If the R-group is aryl or a branched aliphatic group, the 1,3-*anti* product is obtained; however, if the R-group is simply linear, the 1,3-*syn* product is obtained in good diastereoselectivity. Furthermore, the reaction can be carried out under Barbier conditions using allylbromide, and comparable levels of diastereoselectivity are observed. (*R*)-Phenylglycinol has been used as an auxiliary, giving aminal substrates (**1.49**, Scheme 1.9) upon condensation with aromatic aldehydes.[17] When **1.49** is treated with an allylcerium reagent at low-temperature, the imine electrophile is produced *in situ*, furnishing the 1,3-*anti* homoallylic amine product with good diastereocontrol. Subsequent to the allylation, the auxiliary can be cleaved using $Pb(OAc)_4$; however, in some cases racemization occurred.

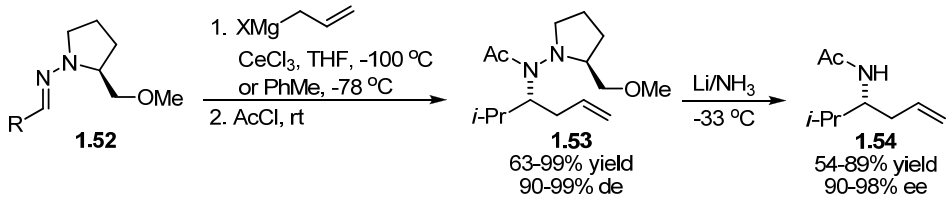
Scheme 1.9: Aminoacid Based Auxiliaries for Imine Allylation



[16] Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766.
[17] Wu, M. –J.; Pridgen, L. M. *Synlett* **1994**, 636.

Ender's SAMP and RAMP hydrazones[18] (**1.52**, Scheme 1.10) have been examined with allylcerium reagents as nucleophiles.[19] Notably, good yields and excellent diastereoselectivities are obtained in the reaction. Furthermore, the N-N bond of the resultant hydrazine products can be readily cleaved, without loss of enantiomeric purity, using Li/NH_3.

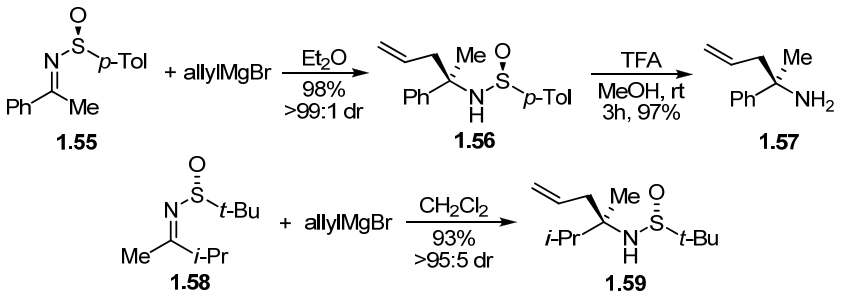
Scheme 1.10: Use of SAMP Hydrazones for Imine Allylation



Chiral sulfinylimines developed by Hua[20] and Ellman[21] undergo efficient allylation with high diastereocontrol when a variety of organometallic reagents are used (Scheme 1.11). Notably, ketimines also undergo allylation with allylmagnesium bromide in excellent diastereoselectivity. In addition, the auxiliary can be cleaved quite readily using strong acid. The *p*-toluenesulfinamide is cleaved using trifluoracetic acid in MeOH, while the *t*-butylsulfinamide is cleaved to the primary amine hydrochloride salt using HCl in MeOH.

[18] Review: Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253.
[19] Enders, D.; Schankat, J.; Klatt, M. *Synlett* **1994**, 795.
[20] Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4.
[21] Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883.

Scheme 1.11: Allylation of Chiral Sulfinylketimines

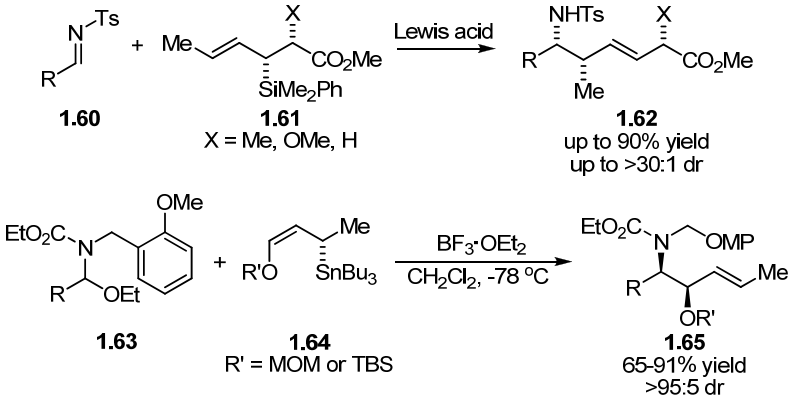


D. Use of Chiral Allylmetals for Diastereoselective Imine Allylation

The methods discussed above for stereocontrol in imine allylation reactions all use chirality on the imine electrophile to control the configuration of the forming C-N stereocenter. Introduction of chirality onto the allylmetal nucleophile is another important approach to control the facial selectivity in imine allylation reactions. Optically active allylic silanes[22] and allylic stannanes[23] have been prepared by the Panek and Marshall groups, respectively (Scheme 1.12). In the case of allylic silane **1.61**, Lewis acid induced allylation provides aminoester **1.62** in good yield with high chirality transfer. An important feature is that the reactive acylimine electrophile intermediate can be produced *in situ* by condensation of an amine or carbamate with an aldehyde; the pre-formation of imine **1.60** is not required. Marshall's stannane (**1.64**) gives excellent chirality transfer in the Lewis acid-induced allylation of aminal **1.63** by reaction through an acyliminium ion.

[22] (a) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1994**, *59*, 2674. (b) Schaus, J. V.; Jain, N.; Panek, J. S. *Tetrahedron* **2000**, *56*, 10263.
[23] Marshall, J. A.; Gill, K.; Seletsky, B. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 953.

Scheme 1.12: Chiral Allylic Silanes and Stannanes for Diastereoselective Imine Allylation

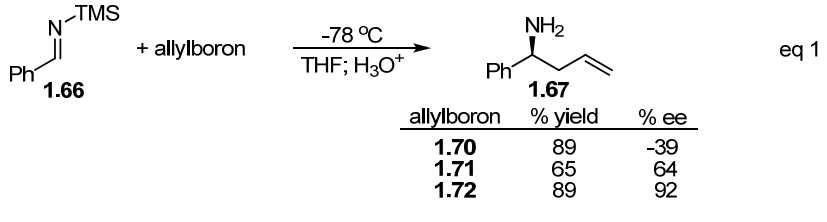


While the synthesis of optically active allylic silanes and stannanes, as in **1.61** and **1.64**, is somewhat difficult and requires multi-step synthesis, the use of chirality on the ligand scaffold of the allylmetal reagent is a convenient way to control facial selectivity in the allylation of imines. Seminal work in this area was performed by Itsuno.[24] The reaction of *N*-(trimethylsilyl)aldimine **1.66** with the Roush[25] chiral allylboronate (**1.70**) or Brown's[26] allylborane (**1.71**) affords the optically active imine allylation product, albeit in poor enantioselectivity (Scheme 1.13, eq 1).[18a] However, application of the Itsuno allylboronate (**1.72**) gives good enantiocontrol in the allylation of **1.66**.[24b] Subsequently, however, Brown and co-workers[27] showed that water is essential to the allylation of *N*-

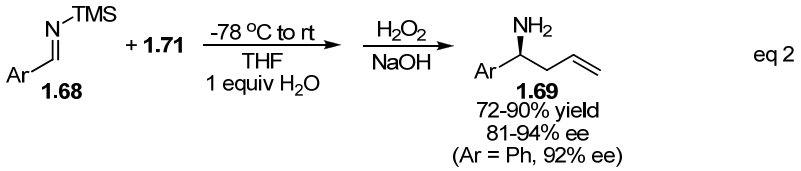
[24] (a) Watanabe, K.; Ito, K.; Itsuno, S. *Tetrahedron Asymm.* **1995**, *6*, 1531. (b) Itsuno, S.; Watanabe, K.; Ito, K.; El-Shehawy, A. A.; Sarhan, A. A. *Angew.Chem. Int. Ed.* **1997**, *36*, 109.
[25] (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316. (c) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117.
[26] Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.
[27] (a) Chen, G. –M.; Ramachandran, P. V.; Brown, H. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 825. (b) Ramachandran, P. V.; Burghardt, T. E. *Chem. Eur. J.* **2005**, *11*, 4387.

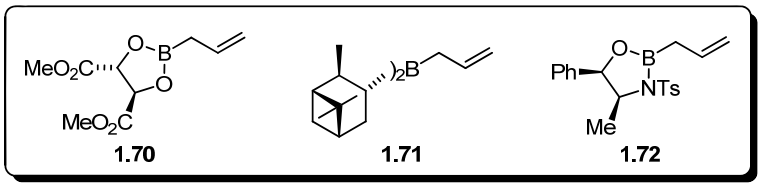
(trimethylsilyl)aldimines (Scheme 1.13, eq 2). The reaction between **1.66** and **1.71** does not occur until water is added. It was rationalized that the role of water was to cleave the weak N-Si bond in **1.66** forming benzaldimine, the reactive electrophile for the allylation reaction, *in situ*. Thus, under the conditions initially explored by Itsuno, the allylation reaction likely takes place during the aqueous workup, which results in poor enantiocontrol when using **1.70** or **1.71**. In support of this hypothesis, it was found that addition of water to **1.66** or **1.68** at -78 ^{o}C in the presence of **1.71** resulted in excellent enantiocontrol in the allylation of aryl substituted silylimines (Scheme 1.13, eq 2).

Scheme 1.13: Asymmetric Imine Allylation with Chiral Allylboron Reagents



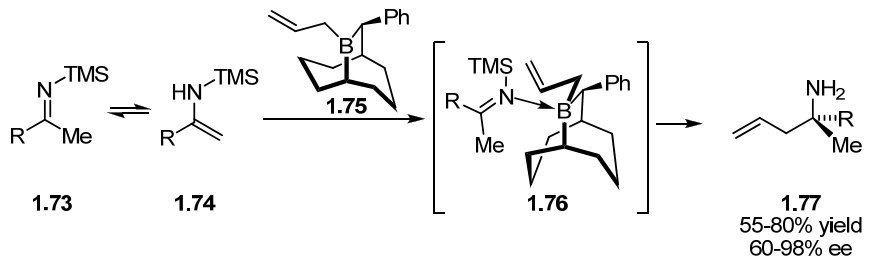
allylboron	% yield	% ee
1.70	89	-39
1.71	65	64
1.72	89	92





Ketimines can also be allylated in good yield with good facial selectivity using Soderquist's allylboronate (**1.75**, Scheme 1.14).[28] Again, *N*-(trimethylsilyl)aldimines do not react with **1.75** without the addition of water; however, the allylation of *N*-(trimethylsilyl)ketimines (**1.73**) proceeds without the addition of water at -78 ^{o}C. Since a mixture of the ketimine along with its enamine tautomer **1.74** are treated with **1.75**, the reaction is argued to proceed via **1.76**, where enamine **1.74** allows access to the more reactive *Z* form of the ketimine. Notably, the homoallylic amine products are isolated in good yields, with moderate to excellent enantioselectivities, and the chiral auxiliary can be recovered.

Scheme 1.14: Asymmetric Allylation of Ketimines with Allylborane 1.75

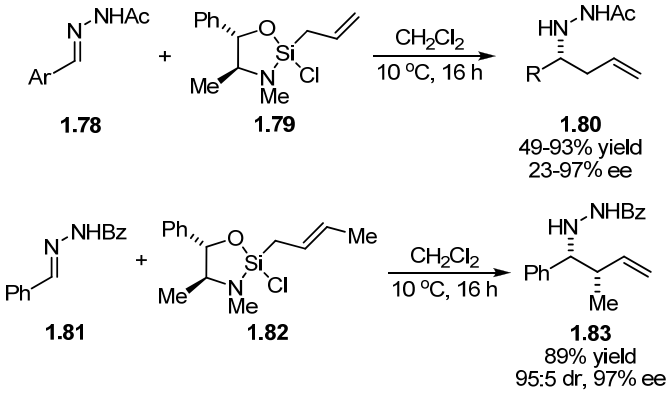


Allylic silanes **1.79** and **1.82** have been applied to the asymmetric allylation and crotylation of hydrazones **1.78** and **1.81**; a reaction which employs strain-induced Lewis acidity (Scheme 1.15).[29] The chiral allylic silanes are readily prepared from the commercially available and relatively inexpensive aminoalcohol pseudoephederine.[30]

[28] Canales, E.; Hernandez, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 8712.
[29] Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596.
[30] Kinniard, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920.

Excellent yields and enantioselectivities are obtained in the allylation of these hydrazones. In addition, crotylation of benzoylhydrazone **1.81** occurs in good diastereoselectivity and enantioselectivity. Furthermore, use of the *Z* version of **1.82** gave the *anti* diastereomer of **1.83** in comparable levels of yield and selectivity. Notably, this methodology has also been applied to the asymmetric allylation of ketone derived benzoyl hydrazones in 46-92% yield and 86-97% ee.[31]

Scheme 1.15: Use of Chiral Allylic Silanes for Asymmetric Imine Allylation and Crotylation

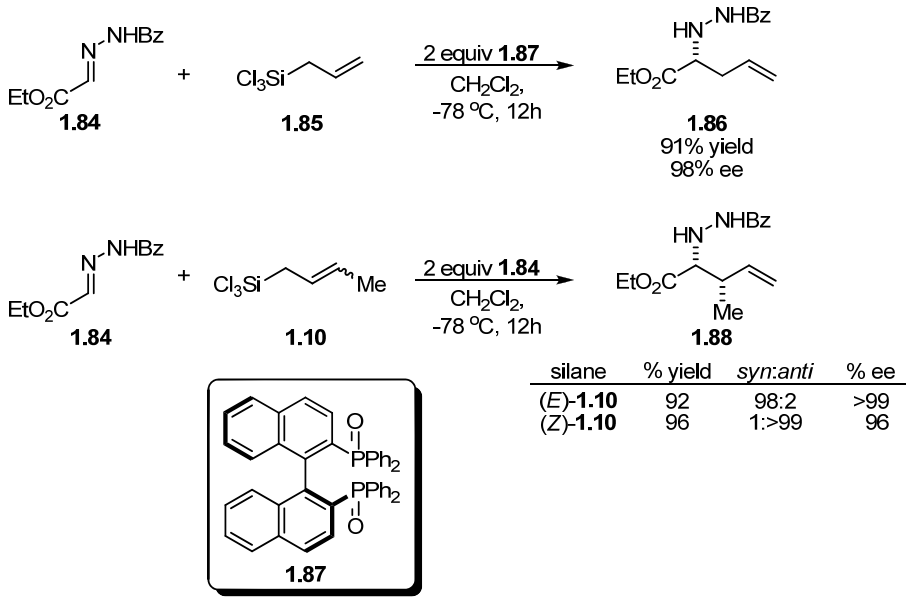


In addition to the use of isolable chiral allyl and crotylmetal reagents, the chiral allylmetal can be generated *in situ* by the addition of a stoichiometric amount of a chiral modifier and an achiral allylmetal. Kobayashi[32] has disclosed the use of BINAP-derived phosphine oxides, in the presence of allyl and crotylsilanes, for the enantio- and diastereoselective allylation and crotylation of hydrazano-esters (**1.84**) with good yields

[31] Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686.
[32] Ogawa, C.; Sugiura, M.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 6491.

and selectivity's (Scheme 1.16). Significantly, the chiral additive can be recovered in near quantitative yield without loss of enantiomeric purity.

Scheme 1.16: Chiral Additives for Asymmetric Imine Allylation and Crotylation



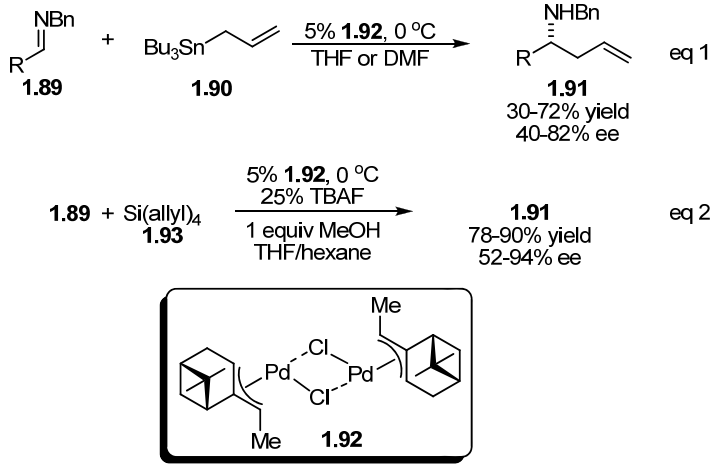
silane	% yield	*syn*:*anti*	% ee
(*E*)-**1.10**	92	98:2	>99
(*Z*)-**1.10**	96	1:>99	96

E. Catalytic Asymmetric Imine Allylation[1b]

All the methods described above require the use of stoichiometric amounts of a chiral group to affect stereoselective imine allylation. If the stereocenter used to control facial selectivity is not wanted in the final product, removal of this group is both time consuming and wasteful. Therefore the use of asymmetric catalysis to control the facial selectivity in the allylation reaction is the most efficient route to chiral amines via allylation. Recent advances in this area are discussed in this section.

Early reports of a catalytic enantioselective allylation of imines were disclosed by Yamamoto using chiral dimeric Pd-catalyst **1.92** and allyltributylstannane (**1.90**, Scheme 1.17, eq 1).[33] While enantioselectivity near 80% ee is obtained with aromatic imines, aliphatic or cinnamyl imines are less selective (40 and 61% ee, respectively). However, these results prompted further studies in this area. Subsequently, Yamamoto was able to apply this same Pd-catalyst to a catalytic asymmetric allylation of imines with tetra(allyl)silane (Scheme 1.17, eq 2).[34] Enantioselectivities and yields are typically improved under these conditions; however, aliphatic and cinnamyl imines are still problematic substrates (52% ee when R = Cy, 74% ee when R = cinnamyl).

Scheme 1.17: Enantioselective Pd-Catalyzed Allyl Additions to Imines



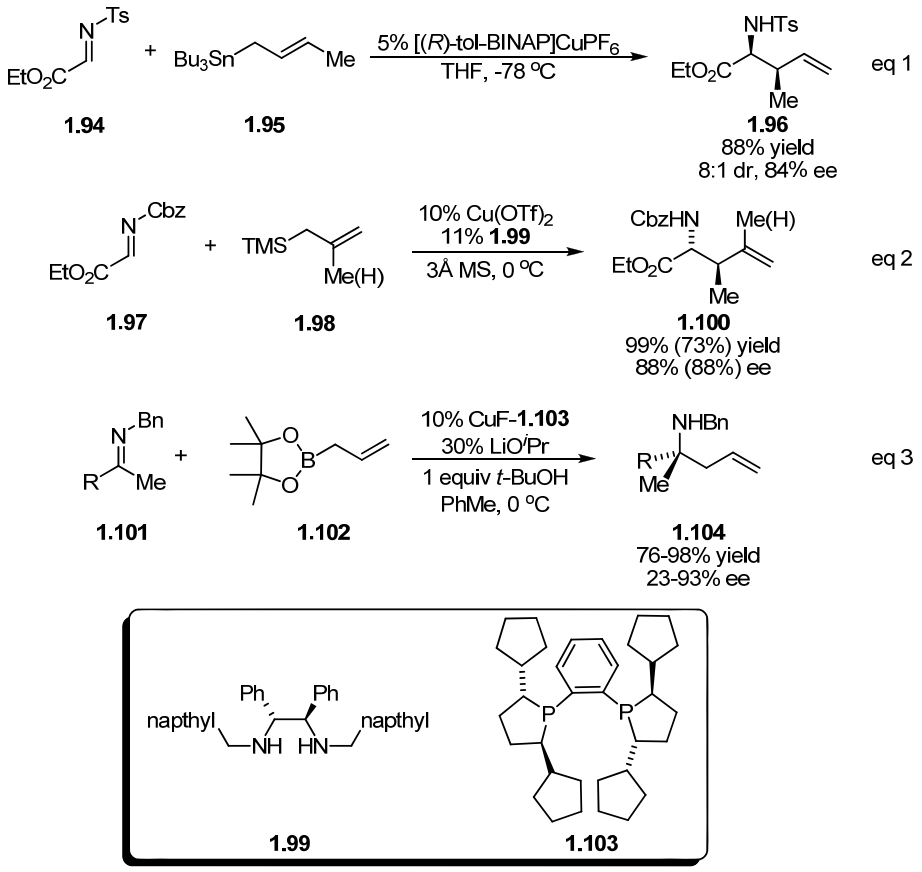
[33] Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242.
[34] Fernandes, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 735.

Copper complexes bearing chiral bis(phosphine) and diamine ligands have been developed as efficient catalysts for asymmetric imine allylation with allylsilane,[35] allylstannane,[35b] and allylborane[36] reagents as nucleophiles. A (*R*)-tol-BINAP derived Cu-catalyst gives effective crotylstannylation of imine **1.94** in good diastereoselectivity and enantioselectivity (Scheme 1.18, eq 1).[35b] Furthermore, various substituted allylsilanes, in the presence of the chiral Cu-catalyst derived from diamine ligand **1.99**, afford the allylation products in good enantioselectivities (Scheme 1.18, eq 2).[35c] Recently, aromatic ketimines were shown to be allylated with the pinacol ester of allylboronic acid (**1.102**) in good enantioselectivities and yields (Scheme 1.18, eq 3).[36] When **1.101** is employed in the reaction with an aliphatic R-group (R = $PhCH_2CH_2$) only 23% ee is observed; however, the reaction is quite efficient, affording the allylation product in 98% yield.

[35] (a) Ferraris, D.; Dudding, T.; Yolung, B.; Drury, III, W. J.; Letka, T. *J. Org. Chem.* **1999**, *64*, 2168. (b) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazelli, R. G.; Jorgenson, K. A. *J. Org. Chem.* **1999**, *64*, 4844. (c) Kiyohara, H.; Nakamura, Y.; Matsubara, R.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 1615.

[36] Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.

Scheme 1.18: Enantioselective Cu-Catalyzed Allyl Additions to Imines

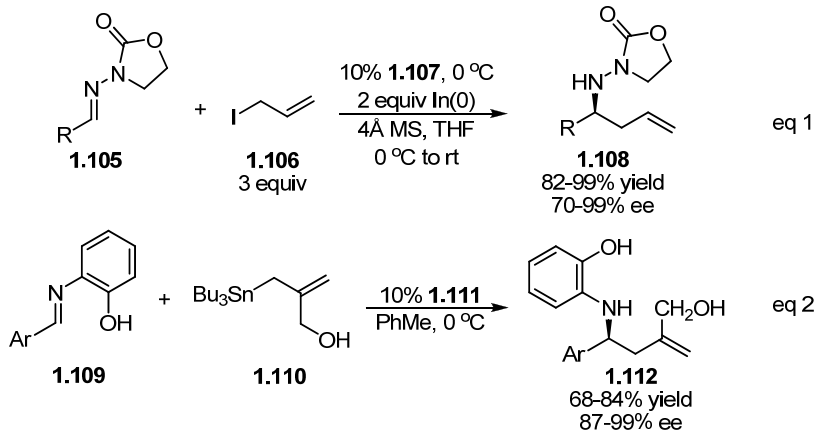


The use of substituted, optically active BINOL derivatives has been exploited for catalytic asymmetric imine allylation. Under Barbier conditions using In-metal and allyl iodide, in the presence of 10% of modified BINOL **1.107**, acylhydrazones (**1.105**) are allylated in good yields and enantioselectivities (Scheme 1.19, eq 1).[37] While aromatic acylhydrazones (**1.105**, R = Ar) give the highest enantioselectivities in the reaction (87-99% ee), an aliphatic acylhydrazone (**1.105**, R = $PhCH_2CH_2$) gave moderate

[37] Kargbo, R.; Takahashi, Y.; Bhor, S.; Cook, G. R.; Lloyd-Jones, G. C.; Shepperson, I. R. *J. Am. Chem. Soc.* **2007**, *129*, 3846.

enantioselectivity (70% ee). In addition, chiral BINOL-derived Zr-catalysts have been developed for the addition of allylstannanes to imines (Scheme 1.19, eq 2).[38] While good enantioselectivities can be obtained using this method, the allylstannane must bear an allylic alcohol moiety in order for high enantioselection to be observed. It should be noted that only aromatic imines were explored using these catalysts.

Scheme 1.19: Substituted Chiral BINOL-Derived Catalysts for Imine Allylation



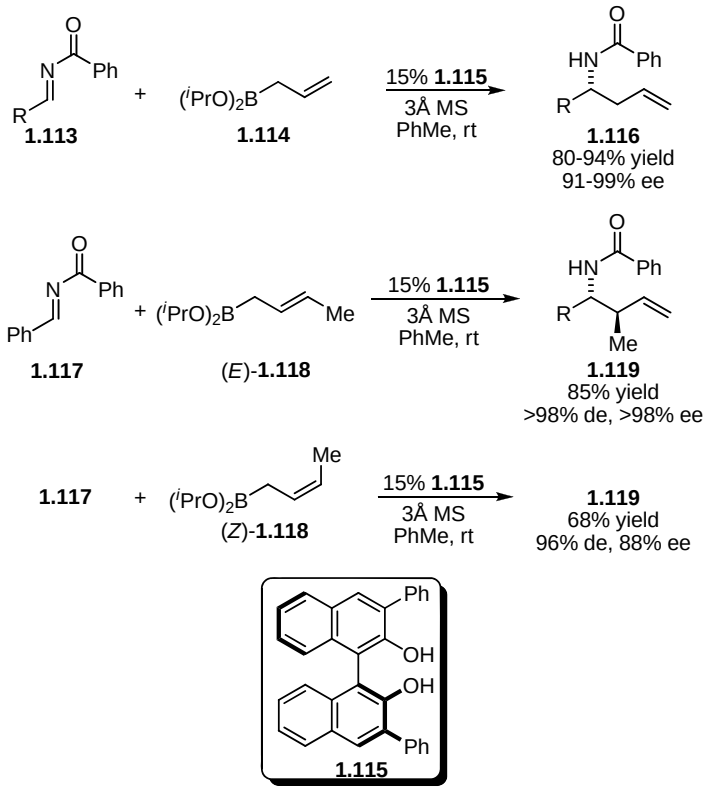
Finally, chiral BINOL-derivatives have been used as organocatalysts for the enantioselective addition of allylboronate and crotylboronate esters to acylimines

[38] Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2001**, *40*, 1896.

(Scheme 1.20).[39,40] Notably, both aromatic and aliphatic imines are allylated in excellent enantioselectivities and yields. Importantly, the crotylation is not stereospecific. That is, when (*E*)-**1.118** is used in the crotylation, high *anti*-selectivity is observed (>99:1 dr), and the use of (*Z*)-**1.118** also preferentially forms the *anti*-diastereomer of product in high selectivity (98:2 dr). The authors rationalize this result by suggesting that the *Z*-configured imine, which is in equilibrium with the more stable *E*-configured imine, is more reactive. The reaction then proceeds through a chair-like transition state when (*E*)-**1.118** is employed, furnishing the *anti*-product. However, when (*Z*)-**1.118** is used as the crotylboronate reagent, the crotylation of the *Z*-configured imine must proceed through a boat-like transition state to afford the *anti*-product. The preference for a boat-like transition state for the crotylation with (*Z*)-**1.118** presumably results from a penalizing *pseudo*-1,3-diaxial interaction between the methyl group on the crotylboronate and the acyl group of the *Z*-configured imine that results from reaction through a chair-like transition state.

[39] Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398.
[40] For seminal work on the use of BINOL-derived allylboronates for use in asymmetric allylation of aldehydes, see: (a) Thormeier, S.; Carboni, B.; Kaufmann, D. E.; *J. Organomet. Chem.* **2002**, *657*, 136. (b) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701.

Scheme 1.20: Organocatalytic Asymmetric Addition of Allyl and Crotylboronates



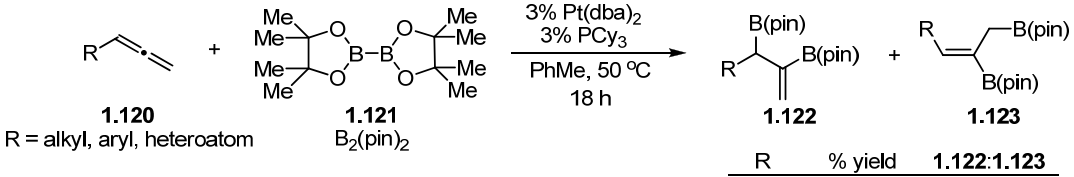
F. Catalytic Diboration of Allenes

The addition of bis(metal) reagents of type M-M or M-M′ to unsaturated carbon-carbon bonds, using transition metal catalysis, is a highly useful process in organic synthesis.[2] Of the group 10 transition metals, Pt has found widespread use as a catalyst in this area.[2d] The first example of an allene diboration was disclosed by Miyaura and co-workers in 1998 (Scheme 1.21).[41] In general, good yields are obtained when commercially available diboron reagent **1.121** is used in the diboration reaction. Regiochemistry in the reaction depends on the substituent on the allene. For alkyl

[41] Ishiyama, T.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1998**, *39*, 2357.

substituted allenes, diboration occurs at the internal olefin of the allene; however, for aromatic or heteroatom substituted allenes, diboration occurs at the external olefin of the allene. $Pt(PPh_3)_4$ is also an effective catalyst for this transformation giving improved yields and regioselectivities in some cases.

Scheme 1.21: Pt-Catalyzed Diboration of Allenes



1.120
R = alkyl, aryl, heteroatom

1.121
$B_2(pin)_2$

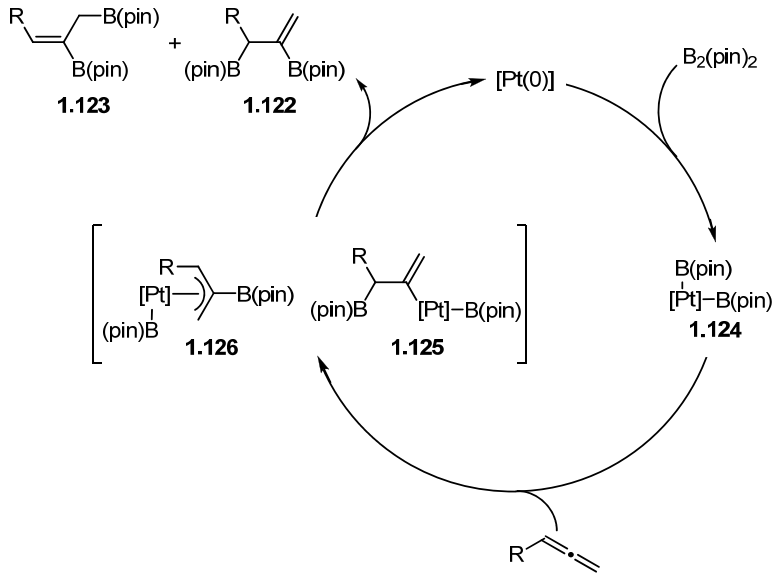
1.122

1.123

R	% yield	**1.122**:**1.123**
Bu	90	84:16
Ph	84	32:68
OMe	85	0:100

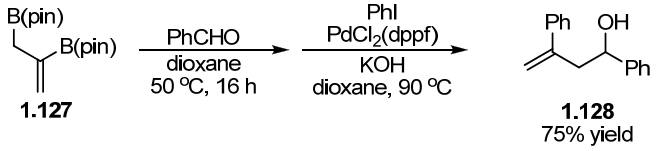
The proposed mechanism for this process is shown in Scheme 1.22. Oxidative addition of $B_2(pin)_2$ to Pt gives diboronate Pt-complex **1.124**. Insertion of the allene then gives rise to complex **1.125** or **1.126**, which upon reductive elimination releases the Pt catalyst and affords product **1.122** or **1.123**.

Scheme 1.22: Miyaura's Proposed Mechanism for the Pt-Catalyzed Diboration of Allenes



The potential for the products of allene diboration to participate in a subsequent allylation reaction has been demonstrated (Scheme 1.23). When benzaldehyde is treated with diboronate ester **1.127** in dioxane, followed by Suzuki-Miyaura cross-coupling[42] with iodobenzene, homoallylic alcohol **1.128** is isolated in good yield. Only diboronate **1.127** has been explored in this type of allylation reaction.

Scheme 1.23: Allylation of Benzaldehyde with a Product of Allene Diboration



[42] Reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Kohta, S.; Lahirir, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

III. Development of the Pd-Catalyzed Enantioselective Diboration of Allenes and its Application to the Allylation of Imines

A. The Pd-Catalyzed Enantioselective Diboration of Allenes[3]

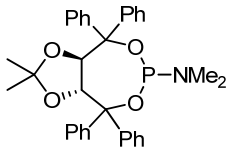
As described in the introduction, the bis(metalation) of the internal olefin of an allene may provide a useful allylboronate for the allylation of imine electrophiles. Precedent from Miyaura's group verifies that these intermediates can be used in aldehyde allylation; however, to access synthetically useful chiral allylboronates, highly regioselective diboration of the internal olefin of the allene must occur. Furthermore, to arrive at optically active allylation products, the diboronate intermediate must be formed in enantiomerically enriched form. Thus, we began to study the allene diboration reaction using chiral phosphine ligands as a means to access chiral allene diboration products with high enantiomeric purity.

Before I joined this project, fellow graduate student Nicholas Pelz had determined that the use of electron-rich phosphines, such as PCy_3, HMPT, or $P(OEt)_3$, in the presence of $Pd_2(dba)_3$, furnished exclusive diboration to the internal olefin of decyl allene in only 1 h at room temperature. This was surprising since Pd-catalyzed diboration reactions are rare.[2e,43] More importantly, after a short screen of chiral phosphine ligands, he and Angela Woodward discovered that the use of (TADDOL)MONOPHOS[44] (**1.129**, Figure 1.2) in the diboration of decyl allene led to product formation with complete regiocontrol

[43] Cui, Q.; Musaev, D.; Morokuma, K. *Organometallics* **1998**, *17*, 742.
[44] (a) Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron Asymm.* **1998**, *9*, 2409. (b) Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Manganey, P. *Tetrahedron Lett.* **1998**, *39*, 7869.

in good yield and enantioselectivity. It was at this point that I joined this project and was involved in examining the substrate scope of the allene diboration reaction.

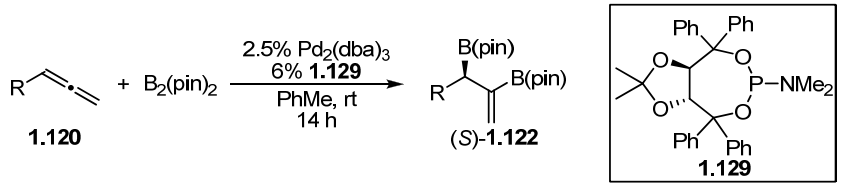
Figure 1.2: Structure of (TADDOL)MONOPHOS



1.129

The substrate scope in the asymmetric Pd-catalyzed allene diboration is shown in Table 1.3. Diboration of either aromatic or aliphatic allenes occurred at the internal olefin of the allene with complete regiocontrol. Furthermore, the products were purified using silica gel chromatography and isolated in good yield and enantiomeric purity. In general, diboration of aliphatic allenes occurred with higher enantioselectivity, but in lower yields relative to aromatic allenes. In addition, the sterically hindered substrate *t*-butyl allene participated in the reaction; however, longer reaction times were required to afford useful product yields (entry 6).

Table 1.3: Substrate Scope in the Asymmetric Pd-Catalyzed Allene Diboration



1.120 (*S*)-**1.122** **1.129**

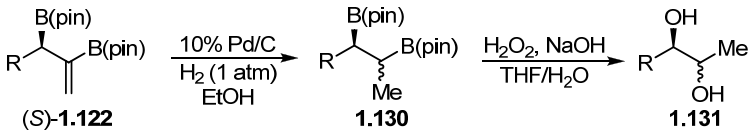
entry	R	% yield[a]	% ee[b]
1	decyl	61	91
2	Cy	62	89
3	$PhCH_2CH_2$	73	90
4	Me	68	92
5	Ph	75	87
6	*t*-Bu	42 (58)[c]	89 (88)[c]
7	$BnOCH_2CH_2$	57	91
8	Bn	65	90

[a]Isolated yield of diboronate ester product. Yield represents an average of 2 experiments in each case. [b]Enantiomeric excess was determined by chiral GLC or SFC analysis of the diol derived from hydrogenation followed by oxidation with H_2O_2. [c]Value in parentheses represents data for a 48 h reaction.

The procedure for determining the enantiomeric purity of the diboronate ester products (**1.122**) from the allene diboration deserves mentioning, as **1.122** could not be directly analyzed by typical methods. Initially, the olefin in **1.122** was hydrogenated using Pd/C and H_2 gas, followed by oxidation of the C-B bonds with alkaline H_2O_2 to afford a diol, as a mixture of diastereomers (Scheme 1.24). The diol products from this reduction/oxidation sequence could then be analyzed using chiral GLC or chiral SFC to determine their enantiomeric purities. Surprisingly, this method gave non-reproducible

results, and the *syn* and *anti* diastereomers of the resultant diols did not possess the same enantiomeric purity.

Scheme 1.24: Enantiomeric Excess Determination of (*S*)-1.122

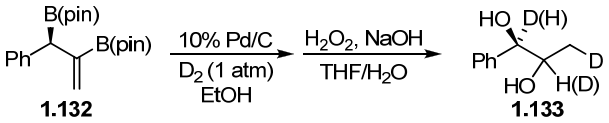


(*S*)-**1.122** **1.130** **1.131**

Heterogeneous Pd-catalysts for the hydrogenation of olefins are known to isomerize alkenes during the hydrogenation process.[45] We reasoned that isomerization of (*S*)-**1.122** to a mixture of internal alkene isomers, during the heterogeneous hydrogenation, was the reason for the differences in enantiomeric purity between the two diastereomeric diols formed after oxidation. Since this ultimately leads to deterioration in the enantiomeric purity of **1.130** during the hydrogenation of (*S*)-**1.120**, this method would not give accurate enantioselectivity data for the diboration reaction. To ascertain if β-hydride elimination (presumed mechanism for isomerization) was occurring in the hydrogenation of (*S*)-**1.122** with Pd/C, diboronate ester **1.132** was subjected to the hydrogenation conditions using D_2 gas in place of H_2 (Scheme 1.25). Deuterium scrambling was observed in the resultant diols, indicating that β-hydride elimination was likely occurring during the hydrogenation.

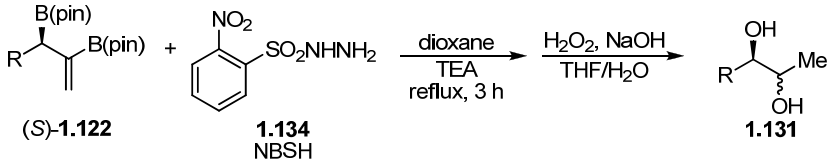
[45] Siegel, S. Heterogeneous Catalytic Hydrogenation of C=C and C≡C. In *Comprehensive Organic Synthesis*; Fleming, I., Trost, B. M. Eds.; Pergamon Press: New York, 1991; Vol. 8, pp 417-442.

Scheme 1.25: Hydrogenation of (*S*)-1.132 with D_2



This problem was easily solved by conducting the hydrogenation with diimide (Scheme 1.26).[46] Diimide is known to reduce olefins through a concerted process via *syn* addition of H_2 with concomitant loss of N_2. NBSH[47] was used to produce diimide *in situ* for the reduction of (*S*)-**1.122**.[48] After oxidation with H_2O_2, the resultant diastereomeric diols had the same enantiomeric purity, and reproducible results could be obtained.

Scheme 1.26: Diimide Reduction of (*S*)-1.122



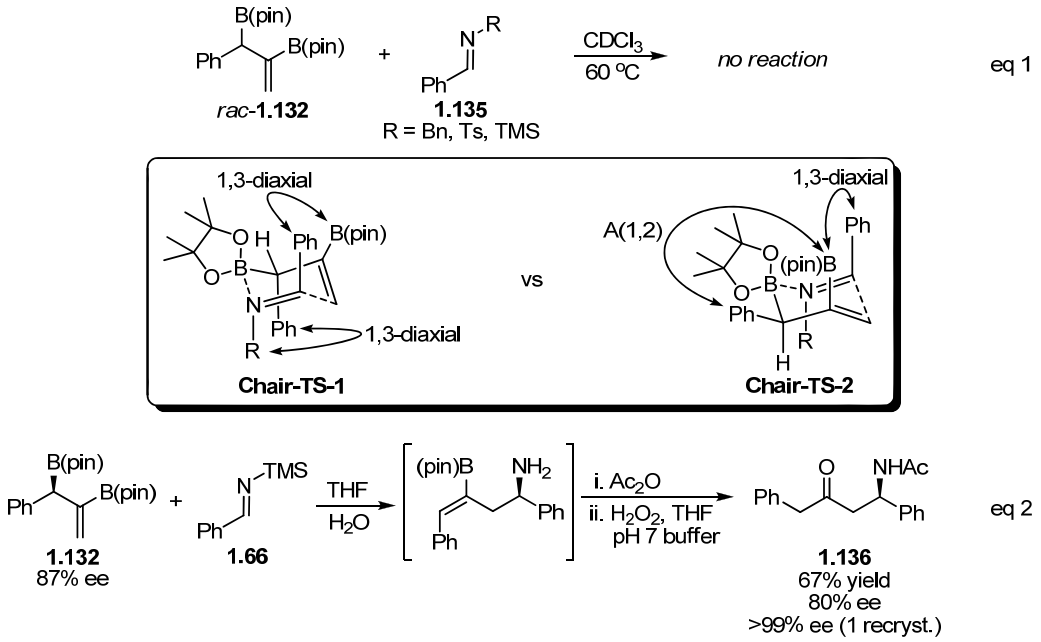
B. Allylation of Imines with the Products of Allene Diboration

With access to enantiomerically enriched diboronate esters from the diboration of allenes, the use of these reagents in allylation reactions with imines could now be explored. Initially, the reaction between diboron **1.132** and (*E*)-aldimines (**1.135**) was

[46] (a) Corey, E. J.; Mock, W. L.; Pasto, D. J. *Tetrahedron Lett.* **1961**, 347. (b) Corey, E. J.; Pasto, D. J.; Mock, W. L. *J. Am. Chem. Soc.* **1961**, *83*, 2957. (c) Review: Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91.
[47] (a) Dann, A. T.; Davies. W. *J. Chem. Soc.* **1929**, 1050. (b) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.
[48] (a) Haukaas, M. H.; O'Doherty, G. H. *Org. Lett.* **2002**, *4*, 1771. (b) Hunig, S.; Muller, H. R.; Their, W. *Angew. Chem. Int. Ed.* **1965**, *4*, 271.

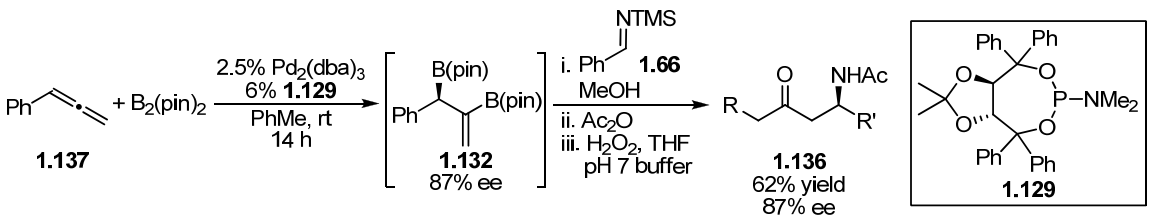
examined (Scheme 1.27, eq 1). No reaction was observed with benzyl, tosyl, or silyl-substituted imines, even after heating to 60 ^{o}C. Considering the chair-like transition structures **Chair-TS-1** and **Chair-TS-2** as possible reaction pathways for the desired allylation reaction, it was postulated that **1.135** was inert to allylation because of the high steric demands present in **Chair-TS-1** and **Chair-TS-2**. In an attempt to alleviate strain in the transition state, the ammonia-derived imine of benzaldehyde (**1.135**, R = H) was employed. This imine could be generated *in situ* from imine **1.66** by protodesilylation with water (Scheme 1.27, eq 2). ^{1}H NMR analysis of this reaction indicated that the starting material was completely consumed. Subsequently, the allylation product was acylated, and oxidized with buffered H_2O_2 to give β-amidoketone **1.136**. Notably, the reaction occurred with a high level of chirality transfer in good yield, with >99% ee material being obtained after one recrystallization.

Scheme 1.27: Initial Attempts at Imine Allylation with 1.132



To make this process more efficient, development of a single-flask tandem allene diboration/imine allylation was pursued to obviate the need for isolation of the diboronate ester intermediate. Gratifyingly, treatment of the unpurified allene diboration reaction mixture with silylimine **1.66** and 1.1 equiv of MeOH, followed by acetylation and buffered oxidation, led to formation of β-amidoketone **1.136** in excellent overall yield with complete chirality transfer (Scheme 1.28). These conditions proved to be general, and the substrate scope is described in Section C of this chapter (see page 39).

Scheme 1.28: Tandem Allene Diboration/Imine Allylation

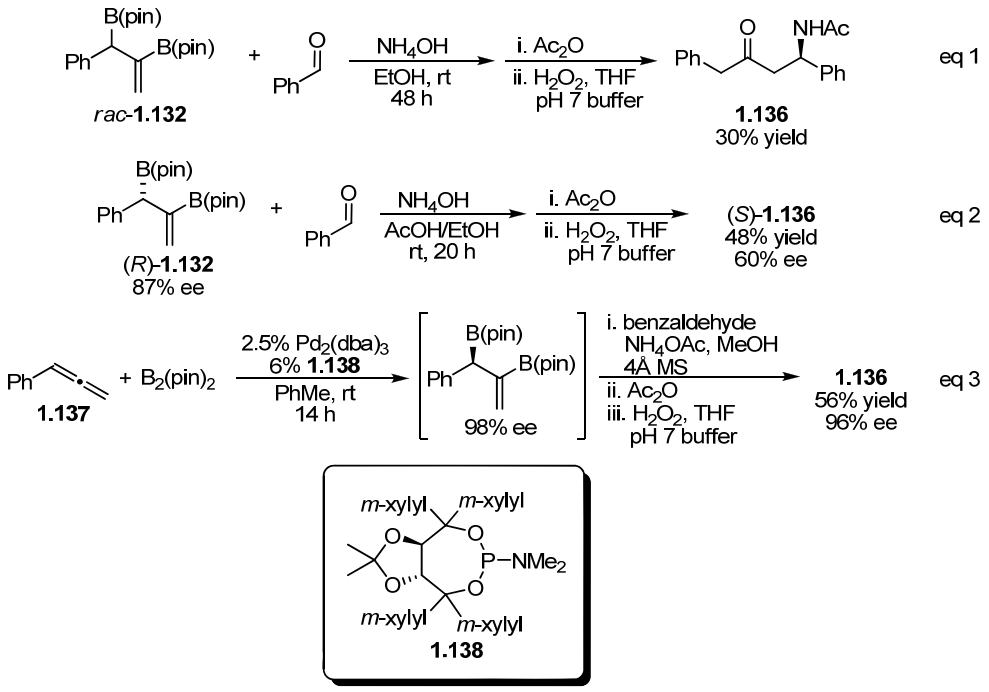


In addition to protonolysis of silyl-derived imines, direct condensation of benzaldehyde with an ammonia source provides access to reactive N-H substituted aldimines. Use of this procedure for imine allylation with the products of allene diboration would obviate the need for synthesizing and isolating the imine electrophile. As noted previously, Kobayashi[8] has developed this protocol for imine allylboration, where the imine is formed *in situ* by reaction of an ammonia source with an aldehyde. In his report, the ammonia source consists of either liquid NH_3 in EtOH or a 28-30 wt% ammonium hydroxide solution in EtOH. In our initial experiments, a solution of diboronate ester **1.132** was added to a stirred solution of benzaldehyde in an ethanolic solution of liquid NH_3 or 29 wt% NH_4OH according to Kobayashi's procedure. It appeared as if some imine allylation product was present in the ^1H NMR spectrum of the unpurified reaction mixture when NH_4OH was used as the ammonia source. However, after acetylation and oxidation, only a 30% yield of the desired β-amidoketone product was isolated (Scheme 1.29, eq 1). Further analysis of the ^1H NMR spectrum of the unpurified reaction mixture, before acetylation and oxidation, suggested that unreacted diboronate ester **1.132** was present. However, the chemical shifts for the benzylic proton in **1.132** and one of the olefinic protons were shifted slightly downfield. Furthermore,

when **1.132** was mixed with 29 wt% NH_4OH in EtOH overnight, these same resonances shifted downfield in the ^1H NMR spectrum. These observations may be explained by a change in the ligand environment around the B-atom in **1.132**, possibly by interaction of hydroxide or ammonia with the vacant orbital on boron. This interaction may decrease the reactivity of **1.132** by blocking the vacant orbital on boron that is needed for coordination to the imine electrophile in the allylation reaction. We postulated that if hydroxide was the culprit, then this problem could be avoided with the use of NH_4OAc, since the acetate ion is less basic and nucleophilic relative to hydroxide. This hypothesis was initially examined by performing the reaction as before, using an ethanolic solution of 29 wt% NH_4OH, but with an equimolar amount of AcOH relative to NH_4OH added to the mixture (Scheme 1.29, eq 2). While the yield did improve, chirality transfer was poor. However, when NH_4OAc was used directly (in MeOH with activated 4 Å molecular sieves), good yield and chirality transfer was obtained (Scheme 1.29, eq 3).[49] Notably, the unpurified allene diboration reaction mixture was employed, obviating the need to purify the diboronate ester nucleophile. The scope of this method is described in the next section (see page 40).

[49] The ligand used in the diboration reaction (**1.138**, Scheme 1.26, eq 3) was identified by Heather Burks in the group to give improved enantioselection in the allene diboration. See: Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5505 and reference 3b.

Scheme 1.29: Allylation of *in situ* Prepared Imines with 1.132

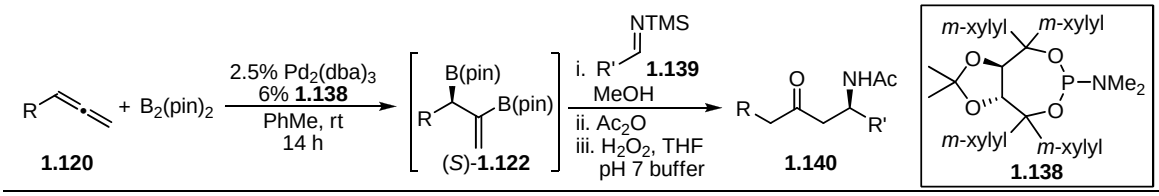


C. Scope of the Tandem Allene Diboration/Imine Allylation and Other Transformations

The scope of the tandem asymmetric allene diboration/imine allylation of silyl-derived imines is given in Table 1.4. It should be noted that while this method was being optimized, phosphoramidite ligand **1.138** was identified by Heather Burks in the group to give enhanced enantioselectivity in the diboration reaction, and therefore, this ligand was now used in the allene diboration.[49] Both aromatic and aliphatic allenes were effective in the tandem diboration/allylation, and good yields were obtained (~60-70%). The only exception was the reaction employing cyclohexyl allene and *N*-(trimethylsilyl)benzaldimine (entry 7). Considering that four reactions are carried out

consecutively in one flask (diboration, allylation, acetylation, and oxidation), the yield per step is >87%. Importantly, only imines devoid of α-protons could be used, since the synthesis of *N*-silyl imines having α-protons is an unsolved problem. However, an aliphatic, α,β-unsaturated imine could be prepared and allylated in good yield and selectivity (entries 3, 6, and 9). In general, the conservation of ee (% cee) was the lowest for this imine electrophile.[50]

Table 1.4: Tandem Allene Diboration/Imine Allylation of Silylimines



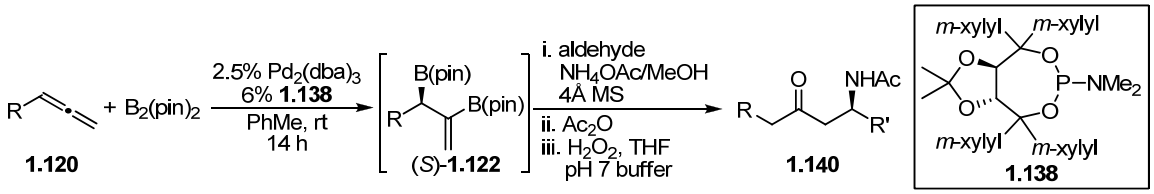
entry	R	R′	% yield[a]	% ee[b,c]	% cee[d]
1	Ph	Ph	68	97	99
2	Ph	2-furyl	68	97	99
3	Ph	(*E*)-hexenyl	70	92	94
4	$PhCH_2CH_2$	Ph	64	93	95
5	$PhCH_2CH_2$	2-furyl	69	92	94
6	$PhCH_2CH_2$	(*E*)-hexenyl	70	89	91
7	Cy	Ph	46	91	98
8	Cy	2-furyl	66	92	99
9	Cy	(*E*)-hexenyl	59	87	94

[a]Yield of β-amidoketone after silica gel chromatography; average of 2 experiments in each case. [b]Enantiomeric excess determined by chiral HPLC or SFC analysis of the β-amidoketone. [c]Enantiomeric purity for the diboron intermediate for R = Ph, $PhCH_2CH_2$, and Cy was 98, 98, and 93% ee, respectively. [d]Defined as (% ee **1.140** ÷ % ee **1.122**) x 100.

[50] The term conservation of ee (cee) was introduced by Evans and co-workers. See: Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761.

Imines prepared *in situ*, from the condensation of an aldehyde with NH_4OAc in MeOH, were examined in the tandem diboration/allylation (Table 1.5). In general, comparable levels of chirality transfer were observed employing this method; however, yields were somewhat lower. In the case of cyclohexyl allene, poor yields were obtained, partly due to competitive allylation of the aldehyde present in the reaction pot. Aliphatic aldehydes did not give satisfactory yields (<8% with butyraldehyde) and were not examined further. Since the silyl-derived imines are moisture sensitive and somewhat difficult to prepare and isolate, this process offers a convenient route to access the same allylation products without the need of isolating these sensitive imines.

Table 1.5: Tandem Diboration/Imine Allylation of *in situ* Prepared Imines



1.120 (*S*)-1.122 1.140 1.138

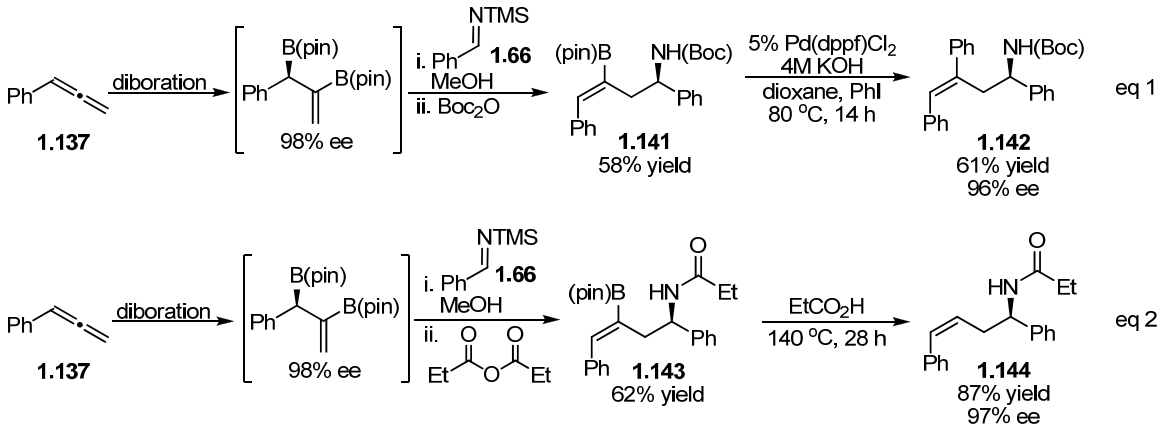
entry	R	aldehyde	% yield[a]	% ee[b,c]	% cee[d]
1	Ph	benzaldehyde	59	96	98
2	Ph	2-furfural	69	96	98
3	$PhCH_2CH_2$	benzaldehyde	59	92	94
4	$PhCH_2CH_2$	2-furfural	56	91	93
5	Cy	benzaldehyde	30	91	98
6	Cy	2-furfural	39	93	100

[a]Yield of β-amidoketone after silica gel chromatography; average of 2 experiments in each case. [b]Enantiomeric excess determined by chiral HPLC or SFC analysis of the β-amidoketone. [c]Enantiomeric purity for the diboron intermediate for R = Ph, $PhCH_2CH_2$, and Cy was 98, 98, and 93% ee, respectively. [d]Defined as (% ee **1.140** ÷ % ee **1.122**) x 100.

A unique feature of the tandem allene diboration/imine allylation product is that it contains a vinylboronate functional group which may be further manipulated. Beside oxidation, as discussed above, this vinylboronate group participated in Suzuki-Miyaura cross-coupling[42] (Scheme 1.30, eq 1); protection of the amine in this sequence with $(Boc)_2O$ gave the Boc-derived vinylboronate ester **1.142** in good yield as one olefin isomer. Suzuki-Miyaura coupling with iodobenzene gave the coupling product **1.142** in good yield and excellent enantiomeric excess. When this coupling reaction was performed using the acetyl protected amine analogous to **1.141**, low yields were obtained, which was presumably due to deprotection of the amine by aqueous KOH during the cross-coupling. Use of the Boc protecting group solved this problem. Aside from oxidation and cross-coupling, the vinylboronate functionality was also protonated in refluxing propionic acid to afford **1.144** (Scheme 1.30, eq 2).[51] This method allows access to *Z*-configured allylation products that can be difficult to prepare by other allylation methods.

[51] (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370. (b) Brown, H. C.; Zweifel, G. J. *J. Am. Chem. Soc.* **1961**, *83*, 3834. (c) Brown, H. C.; Hébert, N. C. *J. Organomet. Chem.* **1983**, *255*, 135.

Scheme 1.30: Access to Other Homoallylic Amides



The olefin geometry of the allylation products was determined by crystallographic analysis of the unprotected amine, and by analysis of the coupling constant of the olefinic protons in **1.144**. To obtain crystals suitable for analysis, the unpurified allene diboration reaction was treated with **1.66** and MeOH to afford allylation product **1.145** (Scheme 1.31). A white solid was obtained that could be purified by crystallization. The X-ray structure of **1.145** (Figure 1.3) verified the configuration of the alkene.

Scheme 1.31: Isolation of the Allylation Intermediate

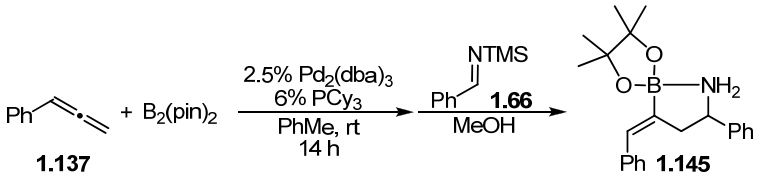
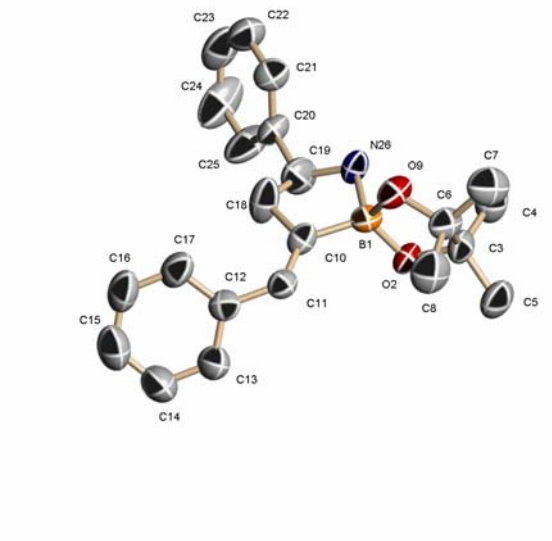


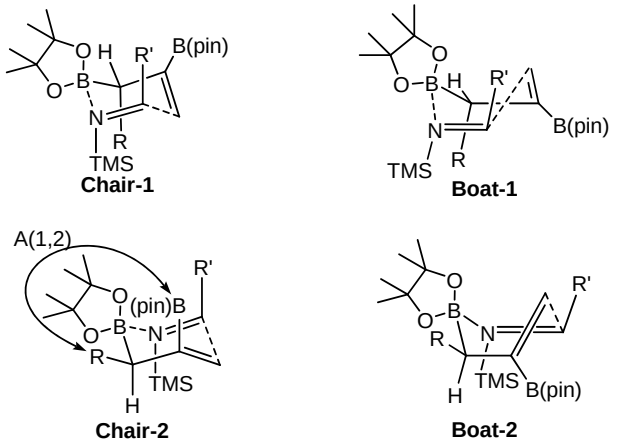
Figure 1.3: Crystal Structure of 1.145



D. Stereochemical Analysis in the Imine Allylation

Considering that allylboron reagents add to aldehyde and imine electrophiles through cyclic transition states,[5] a model for the observed chirality transfer in the imine allylation with allene diboration products could be developed. Upon analysis of the possible cyclic transition states for the reaction of (*E*)-aldimines with diboronate ester **1.122**, it was not surprising that silylaldimines were not reactive until the N-Si bond was cleaved with H_2O or MeOH (Figure 1.4). The possible cyclic transition structures for reaction of **1.122** with an (*E*)-aldimine are shown in Figure 1.4. All possible chair-like and boat-like transition structures have considerable 1,3-diaxial interactions or allylic strain.

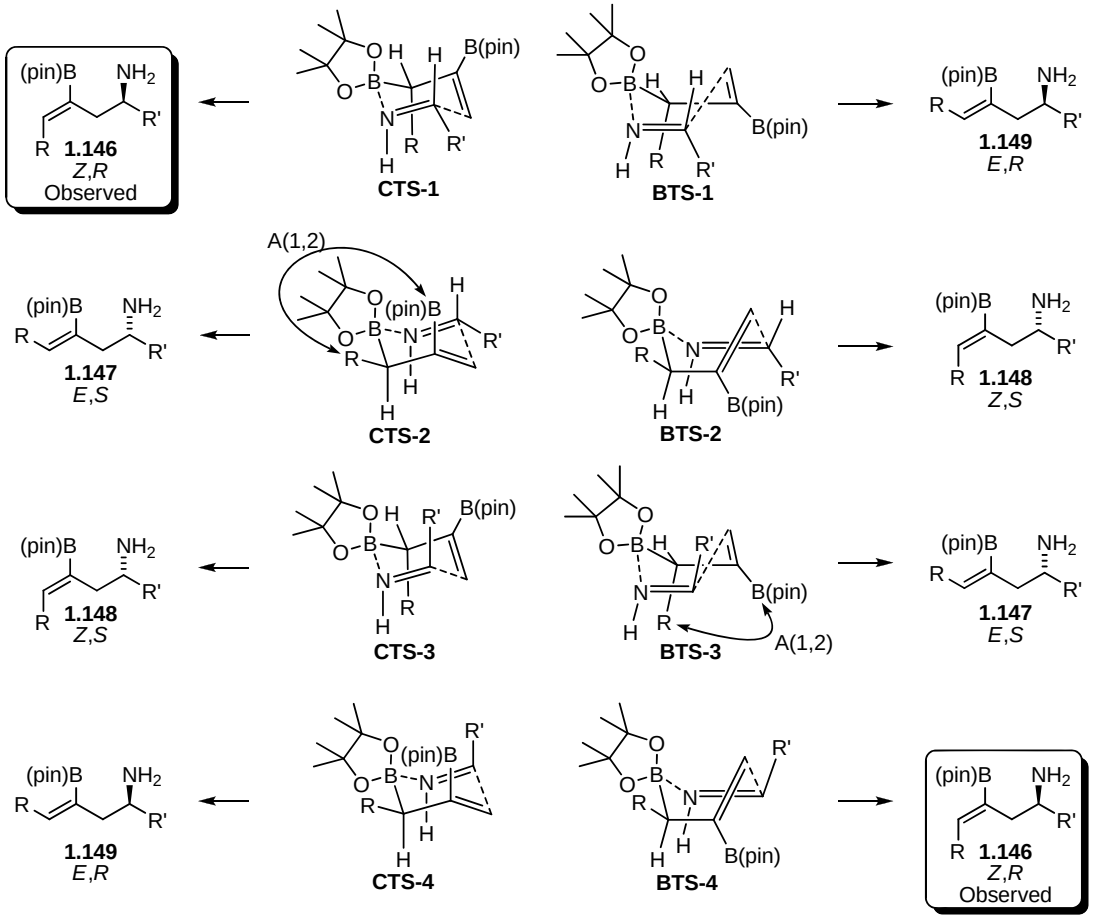
Figure 1.4: Transition Structures for Allylation of (*E*)-Aldimines



Ammonia derived aldimines were required for successful reaction, which presumably is due to a relief in strain exhibited in the allylation transition state. Furthermore, it is likely that these N-H derived aldimines are formed as an *E*/*Z* mixture during the reaction. This then allows for eight possible transition structures for the allylation reaction (Figure 1.5). Transition structures **CTS-1**, **CTS-2**, **BTS-1**, and **BTS-2** represent reaction of the (*Z*)-aldimine, and transition structures **CTS-3**, **CTS-4**, **BTS-3**, and **BTS-4** represent reaction of the (*E*)-aldimine. The only product observed from the allylation reaction is of the *R*-configuration at the newly formed stereocenter and possesses a *Z*-configured alkene. According to the models in Figure 1.5, the allylation reaction product results from either chair-like transition state **CTS-1** or boat-like transition state **BTS-4**. Of the possible transition states for the (*Z*)-aldimine, reaction most likely occurs through **CTS-1**, where the imine substituent resides in an equatorial position, with the substituent on the diboron reagent axial to avoid a penalizing A(1,2) interaction present in **CTS-2**. The (*E*)-aldimine most likely reacts through **BTS-4**. All

other transition states have penalizing 1,3-diaxial or allylic strain. While **BTS-4** correctly predicts the outcome observed in the allylation reaction, the lowest energy pathway is likely reaction of the (*Z*)-aldimine through **CTS-1**. Isomerization between the *E*- and *Z*-aldimines under the reaction conditions may allow for complete product formation through **CTS-1**.

Figure 1.5: Possible Transition Structures in the Imine Allylation



IV. Conclusions

Examination of the substrate scope in the asymmetric Pd-catalyzed allene diboration has been examined. These products were used as allylmetal reagents for imine allylation reactions to furnish atypical allylation products without the need for isolation of the diboronate ester intermediates. The following insights have been gained from this study:

1. Aliphatic and aromatic allenes undergo allene diboration exclusively at the internal olefin of the allene in good yield and with high enantioselectivity.
2. The unpurified diboronate ester products obtained from the allene diboration allylated *N*-(trimethylsilyl)aldimines with excellent chirality transfer when water or MeOH was added to the reaction medium. Subsequent oxidation, protonation, or Suzuki-Miyaura cross-coupling could be carried out in acceptable yield without loss of enantiomeric purity.
3. The unpurified diboronate ester products obtained from the allene diboration allylated ammonia-derived aldimines prepared *in situ* from an aldehyde and NH_4OAc. The chirality transfer for this process was comparable to the analogous reaction employing *N*-(trimethylsilyl)aldimines.
4. A model to explain the stereochemical outcome in the imine allylation has been developed based on cyclic chair-like transition structures.

V. Experimental Procedures

A. General. Melting points were determined using a Mel-Temp II melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker DRX 300 or 400 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the residual solvent resonance as the internal standard ($CHCl_3$: 7.24 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, br = broad, m = multiplet), coupling constants (Hz) and assignment. ^{13}C NMR spectra were recorded on a Bruker 400 spectrometer (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.0 ppm). High-resolution mass spectrometry was performed by the University of Minnesota Mass Spectrometry Service Laboratory. Low-resolution mass spectrometry was performed by the University of North Carolina, Department of Chemistry Mass Spectrometry Facility. Infrared (IR) spectra were obtained on a Nicolet 560 Magna-FTIR. X-ray crystallography was performed by Dr. Peter White of the University of North Carolina X-ray facility.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 X 450 mesh) purchased from Sorbent Technologies. Thin layer chromatography was performed on 250 μm silica gel plates from EMD Chemicals Inc. Visualization was achieved using UV light, phosphomolybdic acid in ethanol, potassium permanganate in water, or cerium sulfate and ammonium molybdate in sulfuric acid, each followed by heating.

Analytical gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a CTC Analysis Combi Pal autosampler by Leap Technologies (Carrboro, NC), a split mode capillary injection system, a flame ionization detector, and a Supelco β-dex 120 column with helium as the carrier gas. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett-Packard Series 1100 liquid chromatograph equipped with a UV detector and a Daicel Chiralcel OD-H column. Analytical supercritical fluid chromatography (SFC) was performed on a Berger Instruments supercritical chromatograph equipped with an Alcott autosampler and a Knauer UV detector.

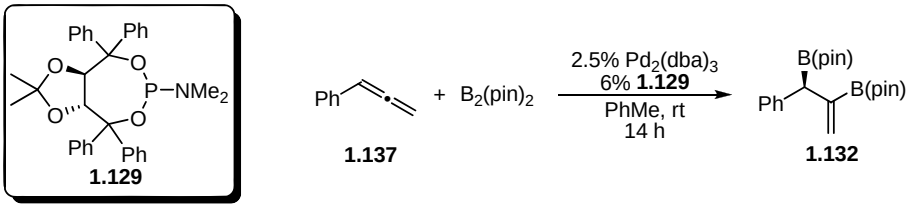
All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Toluene was distilled over CaH_2 and degassed by freeze-pump-thaw cycles prior to use. Anhydrous THF was freshly distilled from Na metal and benzophenone. Tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] and tricyclohexylphosphine were purchased from Strem Chemical Company. (TADDOL)MONOPHOS (**1.129**) was generously donated by Dr. Andre de Vries and Dr. David Ager of DSM Chemical. [(*R*,*R*)-xylylTADDOL]$PNMe_2$ (**1.138**) was synthesized according to the literature.[52] Bis(pinacolato)diboron [$B_2(pin)_2$] was purchased from BASF or Aldrich Chemical Companies and used directly. Allenes were synthesized according to the literature.[53] Aldehydes were purchased from Aldrich Chemical Company and distilled prior to use. *N*-(trimethylsilyl)aldimines were synthesized via the

[52] Boele, M. D. K.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; de Vries, J. G.; van Leeuwen, P. W. M. N.; van Strijdonck, G. P. F. *Chem. Eur. J.* **2004**, *10*, 6232.
[53] Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 112.

known literature procedure[54] and distilled prior to use. Acetic anhydride was purchased from Fisher Chemical and distilled under N_2. All other reagents were purchased from either Fisher or Aldrich Chemical Companies and used directly.

B. Experimental Procedures

Synthesis of Diboronate Ester 1.132



An oven-dried 20 mL scintillation vial, equipped with a magnetic stir-bar, was charged with 9.9 mg (0.011 mmol) of tris(dibenzylideneacetone)dipalladium(0), 13.9 mg (0.0258 mmol) of **1.129**, and 2.7 mL of toluene in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min, and then 131 mg (0.516 mmol) of $B_2(pin)_2$ was added, followed by 50.0 mg (0.430 mmol) of phenyl allene. The vial was capped, taped with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 14 h. Volatile material was removed under reduced pressure, and silica gel chromatography of the mixture afforded 127 mg (0.343 mmol, 80%) of **1.132** as a viscous oil.

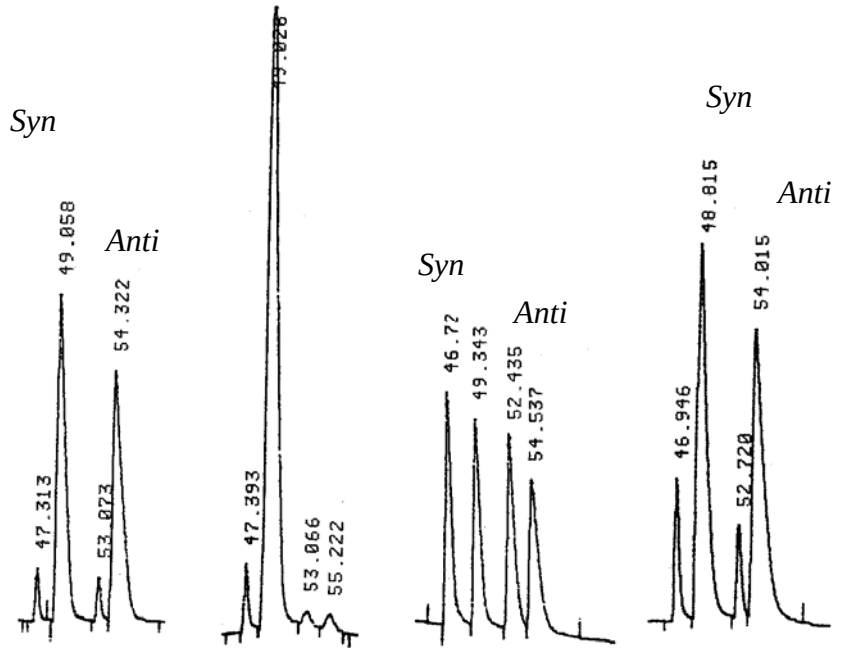
[54] Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157.

(*S*)-4,4,5,5-Tetramethyl-2-[1-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-2-yl]-1,3,2-dioxaborolane (1.132). R_f = 0.22 (15:1 hexanes:EtOAc). IR (neat): 2970 (br, s), 2924 (br, m), 1604 (w), 1417 (br, m), 1313 (br, s), 1142 (br, s) cm^{-1}; ^1H NMR: δ 7.10-7.26 (5H, m, aromatic), 5.81 (1H, br s, CBCH**H**), 5.27 (1H, br s, CBC**H**H), 3.36 (1H, s, ArC**H**B), 1.20-1.25 (24H, m, OCC**H$_3$**); ^{13}C NMR: δ 141.0, 130.4, 128.6, 128.4, 125.8, 83.93, 83.89, 25.38, 25.23, 24.99, 24.93. Carbons with directly attached boron atoms were not observed, most likely due to quadrupolar relaxation.[55] HRMS (ESI) Calcd for $C_{21}H_{32}B_2O_4$ $(M + Na)^+$: 393.2379, Found $(M + Na)^+$: 393.2393.

Proof of stereochemistry. The diboronate ester product was converted to a 1,2-diol using hydrogenation (diimide)/oxidation (Scheme 1.26) and is described on page 54. Analysis of the diols by chiral GLC was used to determine the enantioselectivity of the reaction. Stereochemical ratios were determined in comparison to authentic racemic materials prepared by the diboration of phenylallene using PCy_3 as the achiral ligand, followed by the above reduction-oxidation sequence. The absolute configuration was established in comparison to authentic (1*R*,2*R*)-1-phenylpropane-1,2-diol synthesized via Sharpless asymmetric dihydroxylation of β-methylstyrene.[56]

[55] Wrackmeyer, B. *Prog. NMR Spectrosc.* **1979**, *12*, 227.
[56] Norrby, P-O.; Becker, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1996**, *118*, 35.

Chiral GLC (β-dex, Supelco, 140 °C) analysis of diol products resulting from the reduction-oxidation of ***1.132****:*

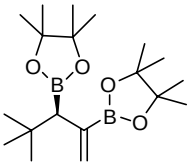


Syn and *anti* diols from diboration product

Authentic *syn* diol

Racemic *syn* and *anti* diols

diols from diboration product + racemic coinjection

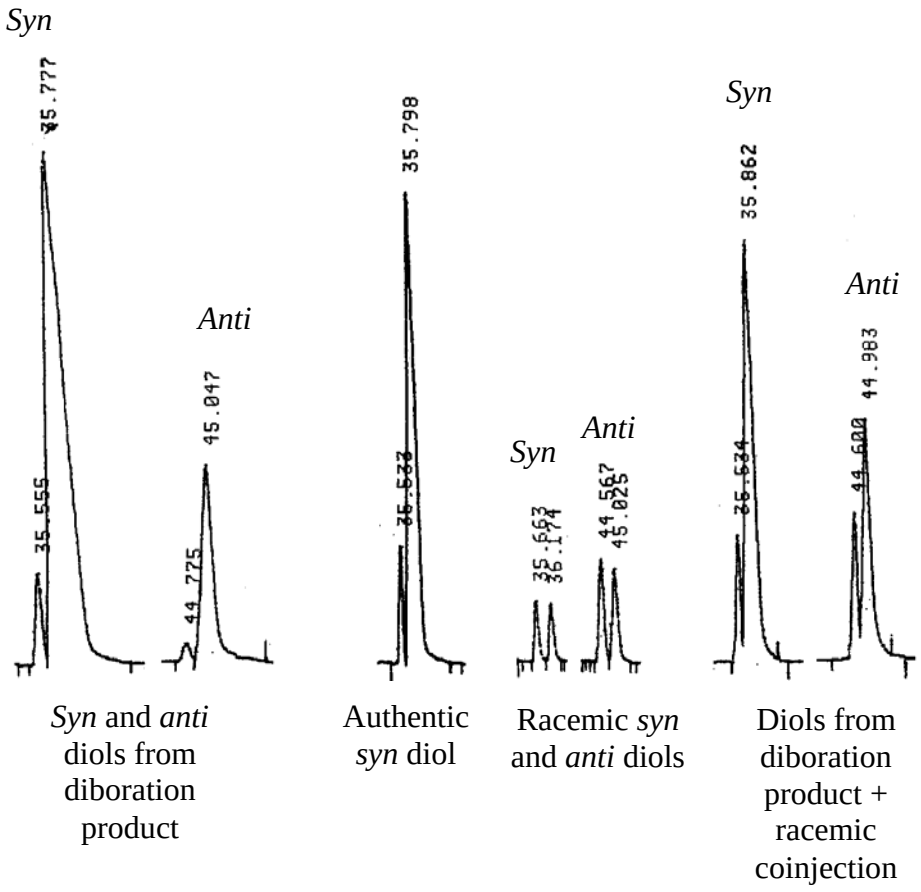


(*S*)-2-[4,4-Dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-2-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.150). The product was prepared according to the general allene diboration procedure used to prepare **1.132** on page 49. A white solid. R_f = 0.21 (15:1 hexanes:EtOAc). IR (KBr pellet): 2986 (br, s), 2943 (br, s), 2866 (br, m) 1926 (w), 1600 (w), 1344 (br, m) cm^{-1}; ^1H NMR: δ 5.89 (1H, d, J = 3.6 Hz, CBCH**H**), 5.71 (1H, d, J = 3.6 Hz, CBC**H**H), 1.96 (1H, s, $(CH_3)_3CB$**H**), 1.17-1.22 (24H, m, OCC**H**$_3$), 0.89 (9H, s, $(C$**H**$_3)_3CB$); ^{13}C NMR: δ 132.5, 83.7, 82.9, 33.4, 29.8, 25.3, 25.2, 25.1, 25.0. Carbons with directly attached boron atoms were not observed, most likely due to quadrupolar relaxation.[53] HRMS (ESI) Calcd for $C_{19}H_{36}B_2O_4$ $(M + Na)^+$: 373.2692, Found $(M + Na)^+$: 373.2701.

Proof of Stereochemistry. The diboronate ester product was converted to a 1,2-diol using hydrogenation (diimide)/oxidation (Scheme 1.26) and is described on page 54. Analysis of the diols by chiral GLC was used to determine the enantioselectivity of the reaction. Stereochemical ratios were determined in comparison to authentic racemic materials prepared by the diboration of *t*-butylallene using PCy_3 as the achiral ligand, followed by the above reduction-oxidation sequence. The absolute configuration was established in comparison to authentic (2*R*,3*R*)-4,4-dimethylpentane-2,3-diol synthesized via Sharpless asymmetric dihydroxylation of (*E*)-4,4-dimethyl-2-pentene.[57]

[57] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **2004**, *94*, 2483.

Chiral GLC (β-dex, Supelco, 80 - 140°C at 1°C/min) analysis of diol products resulting from the reduction-oxidation of ***1.150****:*



Syn and *anti* diols from diboration product

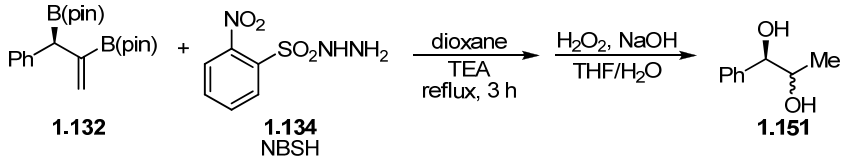
Authentic *syn* diol

Racemic *syn* and *anti* diols

Diols from diboration product + racemic coinjection

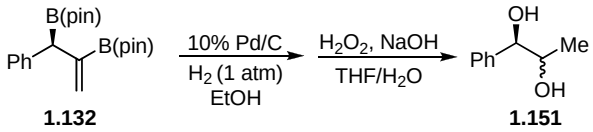
All other allene diboration products listed in Table 1.3 were characterized previously by other group members.[3a]

Representative Procedure for Hydrogenation/Oxidation of the Allene Diboration Products to Assay Enantiomeric Purity



To 40.0 mg (0.108 mmol) of **1.132** in a 20 mL scintillation vial with magnetic stir-bar was added 1.08 mL of anhydrous dioxane in a dry-box. NBSH[47] (235 mg, 1.08 mmol) was added and the vial capped with a septum and removed from the dry-box. Next, 0.23 mL (1.62 mmol) of TEA was added by syringe, and the septum was replaced with a polypropylene cap, sealed with electrical tape, and heated at 95 ^{o}C for 3 h. This mixture was allowed to reach room temperature, and 3 mL of 3 M NaOH was added, followed by slow addition of 1 mL of aqueous 30% H_2O_2. The vial was purged with N_2, loosely capped, and allowed to stir at ambient temperature for an additional 3 h. This mixture was subsequently cooled to 0 ^{o}C and quenched by slow addition of 6 mL of saturated aqueous $Na_2S_2O_3$. The resultant reaction mixture was extracted with EtOAc (3x, ~30 mL). The combined organics were washed with 10 mL of 1M NaOH followed by 15 mL of brine. Finally, drying with anhydrous Na_2SO_4 followed by removal of volatile material under reduced pressure afforded diol **1.151**. The diol was purified by silica-gel chromatography (hexanes/EtOAc), and its structure confirmed by comparison of the ^{1}H NMR spectrum with the literature.

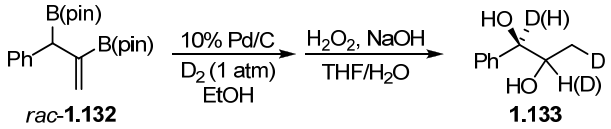
Representative Procedure for Reduction-Oxidation Sequence with Catalytic Pd/C



1.132 **1.151**

A dry 2-dram vial with magnetic stir-bar was charged with 8.6 mg of 10% Pd/C, capped with a septum, and purged with N_2. A solution of 29.8 mg (0.0805 mmol) of **1.132** in 0.4 mL of EtOH was added by canula, and the flask rinsed over with another 0.1 mL of EtOH. The resultant reaction mixture was sparged with H_2, and put under 1 atm of H_2 using a balloon. After 24 h at ambient temperature, the mixture was filtered through a pad of celite and washed with EtOH. To the resulting solution was added 0.25 mL of 3M NaOH, followed by slow addition of 0.15 mL of aqueous 30% H_2O_2. The solution was then left to stir at ambient temperature, under N_2, for 3 h. Finally, the reaction was cooled to 0 ^oC and quenched by slow addition of 2 mL saturated aqueous $Na_2S_2O_3$. Next, 10 mL of 1 M NaOH was added, and this mixture extracted with EtOAc (2x, ~25 mL). The combined organics were washed with brine (1x, 10 mL) and dried with anhydrous Na_2SO_4. Removal of volatile material under reduced pressure afforded an oil, which was purified by silica gel chromatography (hexanes/EtOAc) to afford the diols as a mixture of diastereomers. The structure was confirmed by comparison of the isolated material's ^1H NMR data with that reported in the literature.

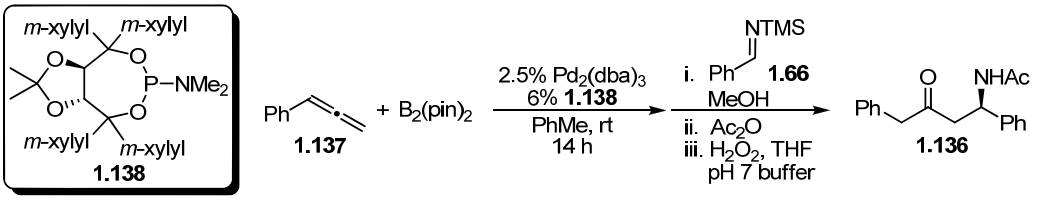
Procedure for Reduction-Oxidation Sequence with Catalytic Pd/C and D_2



rac-**1.132** **1.133**

To 42 mg (0.11 mmol) of *rac*-**1.132** in a dry 2-dram vial with magnetic stir-bar under N_2 was added 0.7 mL of EtOH. Next, 12.1 mg of 10% Pd/C was added, and the reaction mixture was sparged with D_2 and put under 1 atm of D_2 using a balloon. After 17 h at ambient temperature, the mixture was filtered through a pad of celite and washed with EtOH. To the resulting solution was added 0.35 mL of 3 M NaOH followed by slow addition of 0.21 mL of aqueous 30% H_2O_2. The solution was then left to stir at ambient temperature, under N_2, for 3 h. Finally, the reaction was cooled to 0 ^oC and quenched by slow addition of 2 mL saturated aqueous $Na_2S_2O_3$. Next, 10 mL of 1 M NaOH was added, and this mixture extracted with EtOAc (2x, ~25 mL). The combined organics were washed with brine (1x, 10 mL) and dried with anhydrous Na_2SO_4. Removal of volatile material under reduced pressure afforded an oil, which was purified by silica gel chromatography (hexanes/EtOAc) to afford the diols as a mixture of diastereomers.

Representative Procedure for the Tandem Diboration/Imine Allylation with *N*-(Trimethylsilyl)aldimines (Table 1.4)



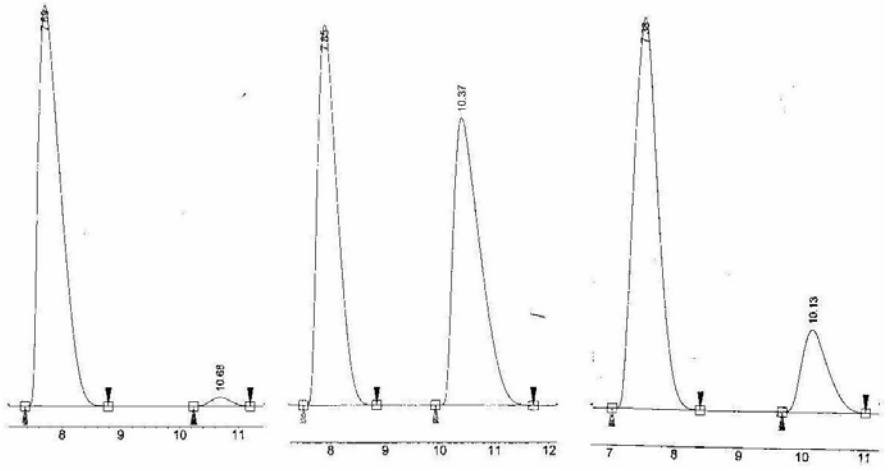
An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 9.9 mg (0.011 mmol) of tris(dibenzylideneacetone)dipalladium(0), 16.8 mg (0.0258 mmol) of **1.138**, and 0.86 mL of toluene in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min; then, 131 mg (0.516 mmol) of $B_2(pin)_2$ was added followed by 50.0 mg (0.430 mmol) of phenyl allene. The vial was capped, sealed with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 14 h. After this time period, the vial was taken back into the dry-box, and 114 mg (0.645 mmol) of *N*-(trimethylsilyl)benzaldimine (**1.66**) was weighed in. Next, 28.7 μL (0.710 mmol) of anhydrous MeOH was added dropwise while stirring the reaction. The vial was capped, removed from the dry-box, and allowed to stir at ambient temperature for 1 h. Next, 0.12 mL (1.3 mmol) of acetic anhydride was added, followed by 0.5 mL of $CHCl_3$. The vial was purged with N_2, sealed with a cap, and left to stir for an additional 1 h. Volatile material was then removed under reduced pressure, and the resulting residue was diluted with 1.6 mL of THF and 1.3 mL of pH 7 buffer. To this solution was added 0.48 mL of aqueous 30% H_2O_2, and the mixture was allowed to stir for 13 h at ambient temperature under N_2. The final mixture was then transferred to a separatory funnel with 25 mL of CH_2Cl_2 and 10 mL of pH 7 buffer. 2 mL of saturated

aqueous $Na_2S_2O_3$ was added, and the organic layer was collected. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organics were washed with 15 ml of brine, dried with anhydrous Na_2SO_4, and concentrated using reduced pressure. Silica gel chromatography (hexanes/EtOAc) of the mixture afforded 80.7 mg (0.287 mmol, 67 %) of (*R*)-*N*-(3-oxo-1,4-diphenylbutyl)acetamide (**1.136**) as a cream-colored solid.

(*R*)-*N*-(3-Oxo-1,4-diphenylbutyl)acetamide (1.136). A cream-colored solid. Mp 123-126 ^{o}C. R_f = 0.17 (1:2 hexanes:EtOAc); IR (KBr): 3312 (br, s), 3060 (br, m), 1953 (w), 1871 (w), 1716 (s), 1650 (s), 1534 (s), 1406 (s), 1367 (s) cm^{-1}; ^{1}H NMR: δ 7.10-7.40 (8H, m, Ar**H**), 7.04 (2H, d, *J* = 6.4 Hz, Ar**H**), 6.63 (1H, br d, *J* = 7.6 Hz, N**H**), 5.37 (1H, q, *J* = 7.6 Hz, ArC**H**N), 3.61 (1H, d, *J* = 16 Hz, ArC$\mathbf{H}_a$H$_b$C(O)), 3.55 (1H, d, *J* = 16 Hz, ArCH$_a$$\mathbf{H_b}$C(O)) 3.08 (1H, dd, *J* = 16 Hz, *J* = 6.0 Hz, C(O)C$\mathbf{H}_a$H$_b$CN), 2.89 (1H, dd, *J* = 16 Hz, *J* = 5.4 Hz, C(O)CH$_a$$\mathbf{H_b}$CN), 1.93 (3H, s, NC(O)C$\mathbf{H_3}$); ^{13}C NMR: δ 207.1, 169.3, 140.6, 133.2, 129.4, 128.7, 128.6, 127.4, 127.1, 126.2, 50.7, 49.5, 46.4, 23.3. LRMS (AP+) Calcd for $C_{18}H_{19}NO_2$ $(M + Na)^+$: 304.1, Found $(M + Na)^+$: 304.3.

Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material prepared by performing the diboration/allylation/acetylation/oxidation procedure using tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was determined by X-ray analysis of (*S*)-2-methyl-*N*-((*R*)-3-oxo-1,4-diphenylbutyl)butanamide (**1.161**, see page 87), which was prepared by using (*S*)-(+)-2-methylbutyric anhydride (>99% ee) in place of Ac_2O in the protection step when using phenyl allene and *N*-(trimethylsilyl)benzaldimine (**1.66**).

*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 5.0 mL/min, 5.0 % MeOH) analysis of β-amidoketone product **1.136**:*

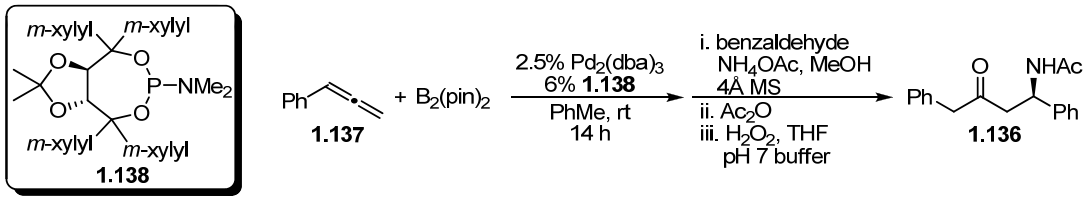


Diboration-allylation-oxidation product

Racemic

Diboration-allylation-oxidation product + racemic coinjection

Representative Procedure for the Tandem Diboration/Imine Allylation with *In Situ* Generated Aldimines (Table 1.5)

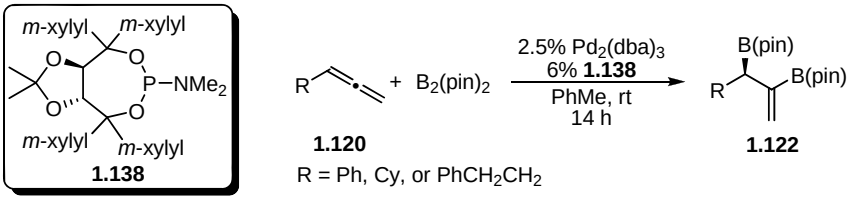


An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 9.9 mg (0.011 mmol) of tris(dibenzylideneacetone)dipalladium(0), 16.8 mg (0.0258 mmol) of **1.138**, and 0.86 mL of toluene in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min; then, 131 mg (0.516 mmol) of bis(pinacolato)diboron was added, followed by 50.0 mg (0.430 mmol) of phenyl allene. The vial was capped, sealed with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 14 h. After this time period, the mixture was taken up in a syringe and added to a solution of benzaldehyde and NH_4OAc in anhydrous MeOH with activated 4 Å molecular sieves that had been stirring under N_2 at room temperature for 2 h (see below for the preparation of this solution). The residue in the vial from the diboration was then rinsed into the aldehyde solution using 0.5 mL of MeOH. This mixture was then allowed to stir for 1 h. Next, 0.41 mL (4.3 mmol) of acetic anhydride was syringed in, and the reaction was allowed to stir for an additional 1 h. The reaction was then poured into 20 mL of Et_2O and filtered over celite until a homogeneous solution was obtained. Volatile material was removed under reduced pressure, and the resulting mixture was then diluted with 1.2 mL of THF and 1.1 mL of pH 7 buffer. To this

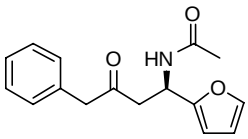
solution was added 0.37 mL of aqueous 30% H_2O_2, and it was then allowed to stir at ambient temperature, under N_2, for 13 h. Lastly, it was worked up as described for the *N*-(trimethylsilyl)aldimine procedure (page 56). Silica gel chromatography (hexanes/EtOAc) of the mixture afforded 74.5 mg (0.265 mmol, 62 %) of (*R*)-*N*-(3-oxo-1,4-diphenylbutyl)acetamide (**1.136**) as a cream-colored solid.

Preparation of the aldehyde solution: To a 5-mL RBF with a magnetic stir-bar and activated 4 Å molecular sieves, in a dry-box under an argon atmosphere, was added 249 mg (3.23 mmol) of NH_4OAc. Next, 0.81 mL of anhydrous MeOH was added, followed by 65.5 μL (0.645 mmol) of benzaldehyde. The flask was capped with a septum, removed from the dry-box, and allowed to stir, under N_2, for 2 h before addition of the unpurified diboration mixture.

Determination of Enantiomeric Purity with Ligand 1.138 in the Allene Diboration for Table 1.4 and 1.5



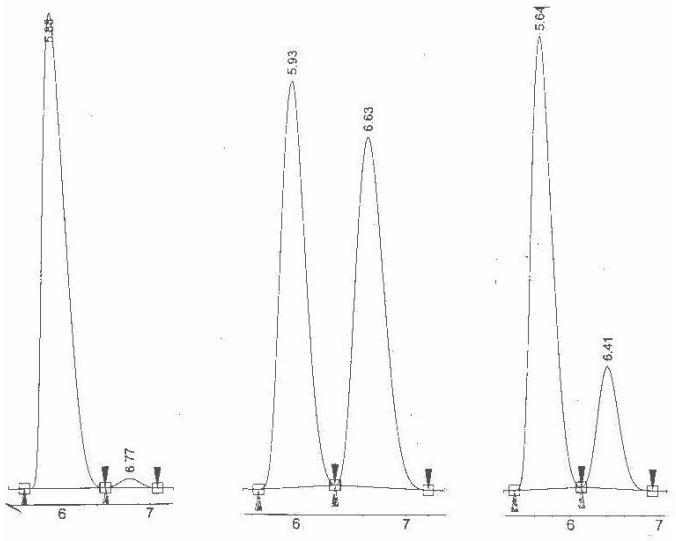
The allene diboration was carried out as described on page 49 using 50.0 mg of allene in 0.86 mL of toluene. Following the same workup procedure, the diboron product was converted to the 1,2-diol, as described on page 54, and analyzed by chiral GLC to determine the enantiomeric purity.



(*R*)-*N*-(1-(Furan-2-yl)-3-oxo-4-phenylbutyl)acetamide (1.152). The product was prepared according to the general allene diboration/imine allylation procedures on pages 57 and 60. A cream-colored solid. Mp 125-127 ^{o}C. R_f = 0.20 (4:1 CH_2Cl_2:Et_2O); IR (KBr): 3293 (br, s), 3064 (br, m), 2901 (m), 2803 (w), 1953 (w), 1712 (s), 1631 (s), 1542 (s), 1363 (s), 1289 (s) cm^{-1}; ^{1}H NMR: δ 7.20-7.45 (4H, m, Ar**H**), 7.15 (2H, d, *J* = 9.6 Hz, Ar**H**), 6.49 (1H, d, *J* = 11 Hz, N**H**), 6.28 (1H, m, Ar**H**), 6.09 (1H, m, Ar**H**), 5.49 (1H, m, ArC**H**N), 3.69 (2H, s, ArC**H$_2$**C(O)), 3.16 (1H, dd, *J* = 22 Hz, *J* = 6.4 Hz, C(O)C**H$_a$**H$_b$CN), 2.90 (1H, dd, *J* = 22 Hz, *J* = 8.0 Hz, C(O)CH$_a$**H$_b$**CN), 1.97 (3H, s, NC(O)C**H$_3$**); ^{13}C NMR: δ 206.7, 169.2, 153.1, 141.7, 133.3, 129.4, 128.8, 127.2, 110.4, 106.2, 50.49, 43.98, 43.83, 23.26. LRMS (AP+) Calcd for $C_{16}H_{17}NO_3$ $(M + Na)^+$: 294.3, Found $(M + Na)^+$: 294.3.

Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material prepared by performing the diboration/imine allylation with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was assumed to be analogous to that obtained for (*R*)-*N*-(3-oxo-1,4-diphenylbutyl)acetamide (**1.136**).

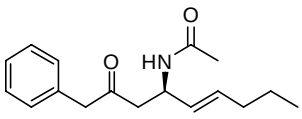
*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 5.0 mL/min, 5.0 % MeOH) analysis of β-amidoketone product **1.152**:*



Diboration-allylation-oxidation product

Racemic

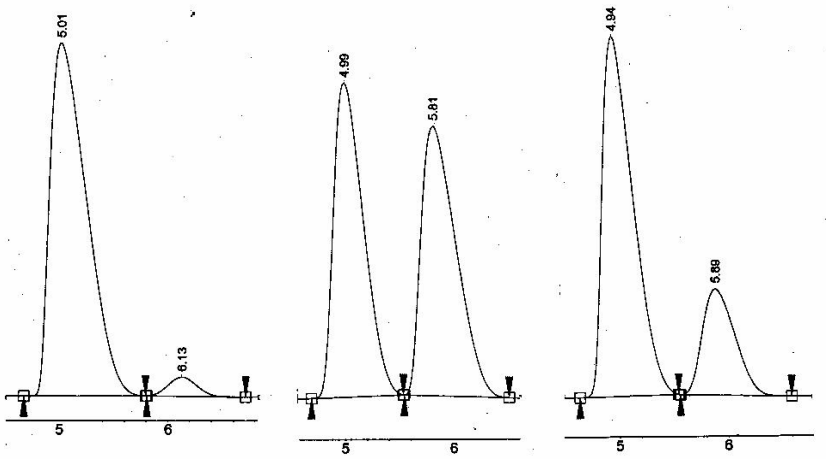
Diboration-allylation-oxidation product + racemic coinjection



(*R*,*E*)-*N*-(2-Oxo-1-phenylnon-5-en-4-yl)acetamide (1.153). The product was prepared according to the general allene diboration/imine allylation procedure on page 57. An off-white solid. Mp 63-67 ^{o}C. R_f = 0.23 (4:1 CH_2Cl_2:Et_2O); IR (KBr): 3293 (br, s), 2963 (br, m), 1712 (s), 1642 (s), 1541 (s), 1413 (m), 1366 (m) cm^{-1}; ^{1}H NMR: δ 7.23-7.45 (3H, m, Ar**H**), 7.18 (2H, d, *J* = 9.6 Hz, Ar**H**), 6.19 (1H, d, *J* = 10 Hz, N**H**), 5.47 (1H, dt, *J* = 15 Hz, *J* = 6.4 Hz, vinyl), 5.35 (1H, dd, *J* = 15 Hz, *J* = 6.4 Hz, vinyl), 4.73 (1H, m, CH=CHC**H**N), 3.69 (2H, s, ArC**H$_2$**C(O)), 2.77 (1H, dd, *J* = 17 Hz, *J* = 4.8 Hz, C(O)C**H$_a$**H$_b$CN), 2.69 (1H, dd, *J* = 17 Hz, *J* = 5.2 Hz, C(O)CH$_a$**H$_b$**CN), 1.75-2.15 (5H, m, allylic C**H$_2$** + NC(O)C**H$_3$**), 1.29 (2H, h, *J* = 7.4 Hz, C**H$_2$**CH$_3$), 0.81 (3H, t, *J* = 7.2 Hz, CH$_2$C**H$_3$**); ^{13}C NMR: δ 207.4, 169.1, 133.4, 132.3, 129.37, 128.7, 128.4, 127.1, 50.54, 47.43, 45.88, 34.08, 23.34, 22.03, 13.51. LRMS (AP+) Calcd for $C_{17}H_{23}NO_2$ (M + Na)$^+$: 296.2, Found (M + Na)$^+$: 296.3.

Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material prepared by performing the diboration/imine allylation with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was assumed to be analogous to that obtained for (*R*)-*N*-(3-oxo-1,4-diphenylbutyl)acetamide (**1.136**).

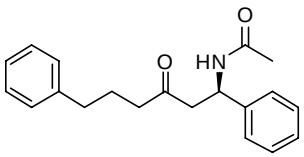
*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 5.0 mL/min, 4.0 % MeOH) analysis of β-amidoketone product **1.153**:*



Diboration-allylation-oxidation product

Racemic

Diboration-allylation-oxidation product + racemic coinjection

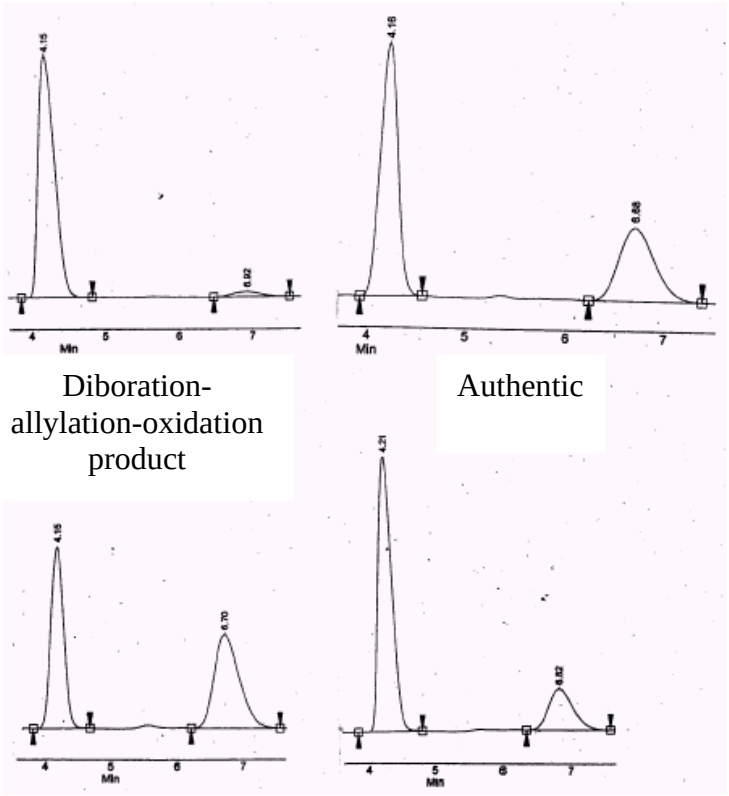


(*R*)-*N*-(3-Oxo-1,6-diphenylhexyl)acetamide (1.154). The product was prepared according to the general allene diboration/imine allylation procedures on pages 57 and 60. A white solid. Mp 111-113 ^{o}C. R_f = 0.16 (1:2 hexanes:EtOAc); IR (KBr): 3351 (br, s), 3025 (br, m), 2932 (br, m), 1949 (w), 1872 (w), 1712 (s), 1646 (s), 1530 (s), 1367 (s), 1281 (s) cm^{-1}; ^{1}H NMR: δ 7.10-7.35 (8H, m, Ar**H**), 7.07 (2H, d, *J* = 7.6 Hz, Ar**H**), 6.61 (1H, d, *J* = 7.6 Hz, N**H**), 5.36 (1H, q, *J* = 6.0 Hz, ArC**H**N), 3.05 (1H, dd, *J* = 16 Hz, *J* = 5.2 Hz, C(O)C**H$_a$**H$_b$CN), 2.83 (1H, dd, *J* = 16 Hz, *J* = 5.6 Hz, C(O)CH$_a$**H$_b$**CN), 2.50 (2H, t, *J* = 7.2 Hz, ArC**H$_2$**), 2.37 (1H, dt, *J* = 17 Hz, *J* = 10 Hz, -CH$_2$C**H$_a$**H$_b$C(O)), 2.26 (1H, dt, *J* = 17 Hz, *J* = 7.2 Hz, -CH$_2$CH$_a$**H$_b$**C(O)), 2.23 (3H, s, NC(O)C**H$_3$**), 1.79 (2H, p, *J* = 7.2 Hz, ArCH$_2$C**H$_2$**); ^{13}C NMR: δ 209.6, 169.3, 141.3, 140.8, 128.6, 128.4, 128.3, 127.4, 126.3, 125.9, 49.54, 47.29, 42.57, 34.74, 24.66, 23.36. LRMS (AP+) Calcd for $C_{20}H_{23}NO_2$ (M + Na)$^+$: 332.2, Found (M + Na)$^+$: 332.4.

Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material prepared by performing the diboration/imine allylation with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was determined by comparison to authentic material prepared by the following sequence (see page 90 for further details). First, the β-amido methyl ester, (*R*)-methyl 3-acetamido-3-phenyl-propanoate (**1.162**), was prepared using asymmetric hydrogenation as described in the literature.[58] This compound was then converted to the Weinreb amide using a procedure employed by Toyooka and Nemoto.[59] Lastly, the amide was converted to the ketone by the addition of (3-phenylpropyl)magnesium bromide using Weinreb's conditions.[60]

[58] Zhou, Y. G.; Tang, W.; Wang, W., B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952.
[59] Toyooka, N.; Okumura, M.; Nemoto, H. *J. Org. Chem.* **2002**, *67*, 6078.
[60] Nahm, S.; Weinreb, S., M. *Tetrahedron Lett.* **1981**, *22*, 3815.

Chiral SFC (AS-H, Chiralpak, 150 bar, 50°C, flow = 5.0 mL/min, 4.0 % MeOH) analysis of β-amidoketone product ***1.154****:*

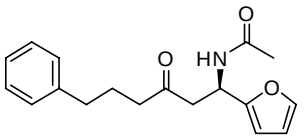


Diboration-allylation-oxidation product

Authentic

Racemic

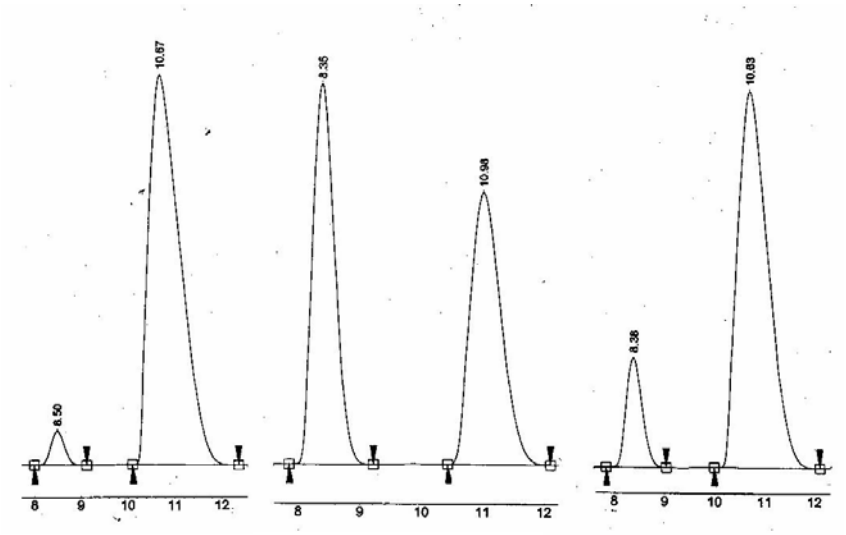
Diboration-allylation-oxidation product + racemic coinjection



(*R*)-*N*-(1-(Furan-2-yl)-3-oxo-6-phenylhexyl)acetamide (1.155). The product was prepared according to the general allene diboration/imine allylation procedures on pages 57 and 60. A cream-colored solid. Mp 86-90 ^{o}C. R_f = 0.22 (4:1 CH_2Cl_2:Et_2O); IR (KBr): 3304 (br, s), 3025 (br, m), 2932 (br, m), 1950 (w), 1872 (w), 1713 (s), 1646 (s), 1522 (s), 1405 (s), 1367 (s), 1297 (s) cm^{-1}; ^{1}H NMR: δ 7.05-7.30 (6H, m, Ar**H**), 6.54 (1H, d, *J* = 8.4 Hz, N**H**), 6.27 (1H, m, Ar**H**), 6.12 (1H, m Ar**H**), 5.44 (1H, m ArC**H**N), 3.06 (1H, dd, *J* = 17 Hz, *J* = 4.8 Hz, C(O)C**H**$_a$H$_b$CN), 2.81 (1H, dd, *J* = 17 Hz, *J* = 6.0 Hz, C(O)CH$_a$**H**$_b$CN), 2.56 (2H, t, *J* = 7.6 Hz, ArC**H$_2$**), 2.38 (2H, m, -CH$_2$C**H$_2$**C(O)), 1.97 (3H, s, NC(O)C**H$_3$**), 1.85 (2H, p, *J* = 6.8 Hz, ArCH$_2$C**H$_2$**); ^{13}C NMR: δ 209.0, 169.2, 153.3, 141.6, 141.3, 128.34, 128.30, 125.9, 110.4, 106.2, 44.78, 43.76, 42.24, 34.78, 24.76, 23.18. LRMS (AP+) Calcd for $C_{18}H_{21}NO_3$ $(M + Na)^+$: 322.1, Found $(M + Na)^+$: 322.3.

Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material prepared by performing the diboration/imine allylation with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was assumed to be analogous to that obtained for (*R*)-*N*-(3-oxo-1,6-diphenylhexyl)acetamide (**1.154**).

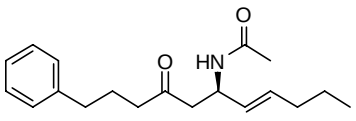
*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 5.0 mL/min, 5.0 % MeOH) analysis of β-amidoketone product **1.155**:*



Diboration-allylation-oxidation product

Racemic

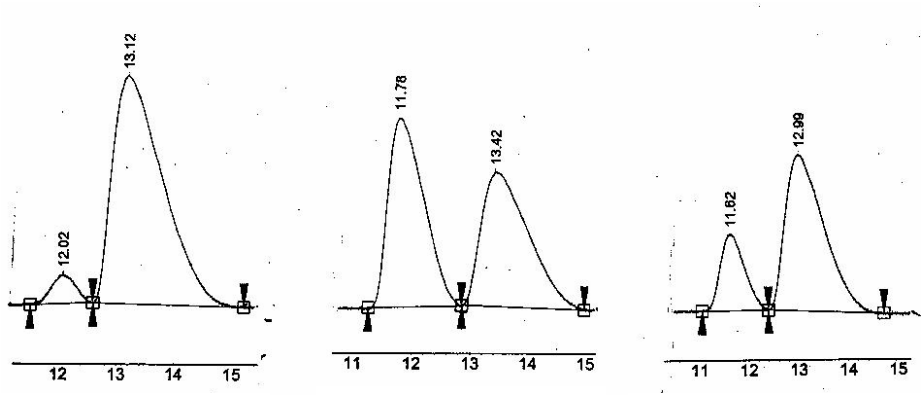
Diboration-allylation-oxidation product + racemic coinjection



(*R,E*)-*N*-(4-Oxo-1-phenylundec-7-en-6-yl)acetamide (1.156). The product was prepared according to the general allene diboration/imine allylation procedure on page 57. A white solid. Mp 62-64 ^{o}C. R_f = 0.25 (4:1 CH_2Cl_2:Et_2O); IR (KBr): 3293 (br, m), 2947 (br, m), 1708 (s), 1650 (s), 1530 (s), 1370 (s) cm^{-1}; ^{1}H NMR: δ 7.10-7.30 (5H, m, Ar**H**), 6.28 (1H, d, *J* = 8.4 Hz, N**H**), 5.54 (1H, dt, *J* = 15 Hz, *J* = 6.8 Hz, vinyl), 5.42 (1H, dd, *J* = 15 Hz, *J* = 6.4 Hz, vinyl), 4.69 (1H, m, CH=CHC**H**N); 2.71 (1H, dd, *J* = 17 Hz, *J* = 4.8 Hz, C(O)C**H**$_a$H$_b$CN), 2.62 (1H, dd, *J* = 17 Hz, *J* = 5.6 Hz, C(O)CH$_a$**H**$_b$CN), 2.58 (2H, t, *J* = 7.6 Hz, ArC**H$_2$**), 2.39 (2H, m, -CH_2C**H$_2$**C(O)), 1.80-2.0 (7H, m, allylic C**H$_2$** + ArCH_2C**H$_2$** + NC(O)C**H$_3$**), 1.32 (2H, h, *J* = 7.2 Hz, C**H$_2$**CH_3), 0.85 (3H, t, *J* = 7.6 Hz, CH_2C**H$_3$**); ^{13}C NMR: δ 210.2, 169.3, 141.5, 133.6, 128.7, 128.6, 128.5, 126.1, 47.78, 433.6, 128.7, 128.6, 128.5, 126.1, 47.78, 46.86, 42.73, 35.09, 34.32, 25.03, 23.62, 22.30, 13.74. LRMS (AP+) Calcd for $C_{19}H_{27}NO_2$ $(M + Na)^+$: 324.2, Found $(M + Na)^+$: 324.4.

Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material prepared by performing the diboration/imine allylation with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was assumed to be analogous to that obtained for (*R*)-*N*-(3-oxo-1,6-diphenylhexyl)acetamide (**1.154**).

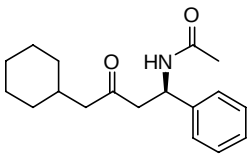
*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 4.0 mL/min, 4.0 % MeOH) analysis of β-amidoketone product **1.156**:*



Diboration-allylation-oxidation product

Racemic

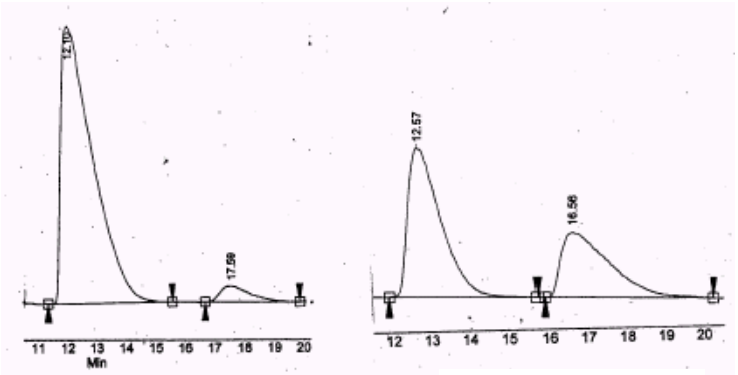
Diboration-allylation-oxidation product + racemic coinjection



(*R*)-*N*-(4-Cyclohexyl-3-oxo-1-phenylbutyl)acetamide (1.157). The product was prepared according to the general allene diboration/imine allylation procedures on pages 57 and 60. A white solid. Mp 90-94 ^{o}C. R_f = 0.26 (4:1 CH_2Cl_2:Et_2O); IR (KBr): 3324 (br, s), 3064 (br, m), 2912 (br, s), 1949 (w), 1704 (s), 1642 (s), 1537 (s), 1413 (m), 1378 (m) cm^{-1}; ^{1}H NMR: δ 7.15-7.40 (5H, m, Ar**H**), 6.74 (1H, d, *J* = 7.6 Hz, N**H**), 5.36 (1H, m, C**H**N), 3.04 (1H, dd, *J* = 16 Hz, *J* = 5.2 Hz, C(O)C**H$_a$**H$_b$CN), 2.82 (1H, dd, *J* = 16 Hz, *J* = 6.0 Hz, C(O)CH$_a$**H$_b$**CN), 2.16 (2H, m, CyC**H$_2$**C(O)), 1.97 (3H, s, NC(O)C**H$_3$**), 1.42-1.75 (6H, m, C$_6$**H**$_{11}$), 1.0-1.35 (3H, m, C$_6$**H**$_{11}$), 0.70-0.90 (2H, m, C$_6$**H**$_{11}$); ^{13}C NMR: δ 209.9, 169.3, 140.9, 128.6, 127.4, 126.3, 51.28, 49.59, 47.63, 33.52, 33.04, 32.94, 26.04, 25.98, 23.37. LRMS (AP+) Calcd for $C_{18}H_{25}NO_2$ $(M + Na)^+$: 310.2, Found $(M + Na)^+$: 310.4.

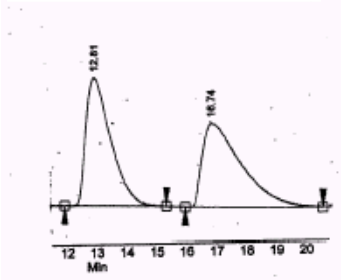
Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material prepared by performing the diboration/imine allylation with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was determined by comparison to authentic material prepared by the following sequence (see page 92 for further details). First, the β-amido methyl ester, (*R*)-methyl 3-acetamido-3-phenyl-propanoate (**1.162**), was prepared using asymmetric hydrogenation as described in the literature.[58] This compound was then converted to the Weinreb amide using a procedure employed by Toyooka and Nemoto.[59] Lastly, the amide was converted to the ketone by the addition of (cyclohexylmethyl)magnesium bromide using Weinreb's conditions.[60]

Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 5.0 mL/min, 3.0 % MeOH) analysis of β-amidoketone product ***1.157****:*

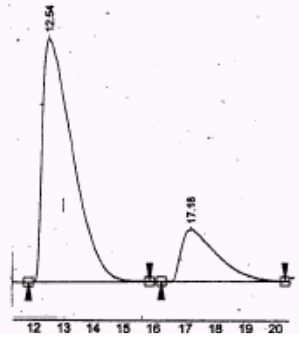


Diboration-allylation-oxidation product

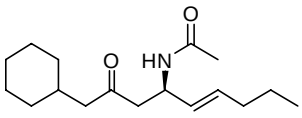
Authentic



Racemic



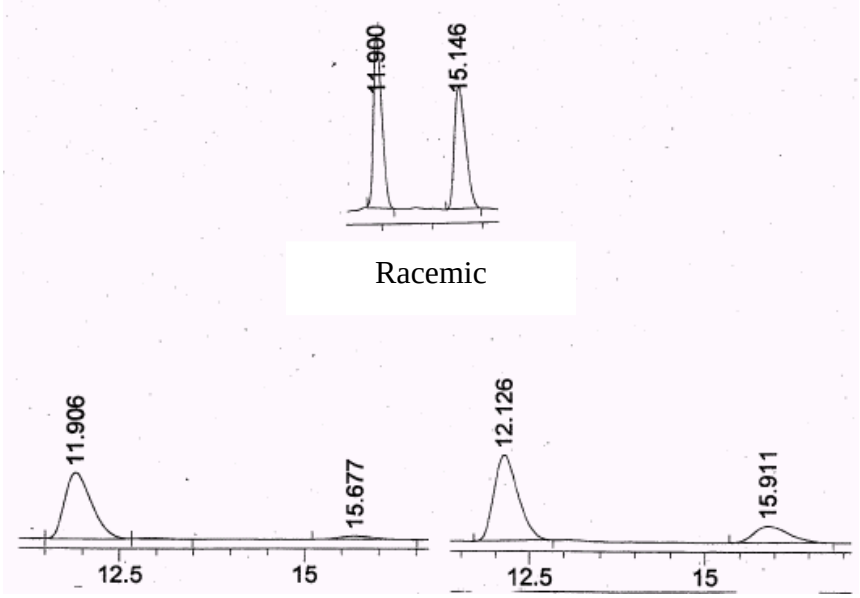
Diboration-allylation-oxidation product + racemic coinjection



(*R*,*E*)-*N*-(1-Cyclohexyl-2-oxonon-5-en-4-yl)acetamide (1.158). The product was prepared according to the general allene diboration/imine allylation procedure on page 57. A cream-colored solid. Mp 61-63 ^{o}C. R_f = 0.19 (4:1 CH_2Cl_2:Et_2O); IR (KBr): 3324 (br, m), 2920 (br, m), 1704 (s), 1627 (s), 1546 (s), 1370 (s), 1293 (s) cm^{-1}; ^{1}H NMR: δ 6.32 (1H, d, *J* = 8.4 Hz, N**H**), 5.53 (1H, dt, *J* = 16 Hz, *J* = 6.4 Hz, vinyl), 5.42 (1H, dd, *J* = 16 Hz, *J* = 6.4 Hz, vinyl), 4.68 (1H, m, CH=CHC**H**N), 2.72 (1H, dd, *J* = 17 Hz, *J* = 4.8 Hz, C(O)C$\mathbf{H_a}H_b$CN), 2.64 (1H, dd, *J* = 17 Hz, *J* = 5.2 Hz, C(O)C$H_a\mathbf{H_b}$CN), 2.23 (2H, d, *J* = 6.8 Hz, CyC$\mathbf{H_2}$C(O)), 1.85-1.97 (5H, m, allylic C$\mathbf{H_2}$ + NC(O)C$\mathbf{H_3}$), 1.76 (1H, m, $C_6\mathbf{H}_{11}$), 1.53-1.69 (5H, m, $C_6\mathbf{H}_{11}$), 1.32 (2H, h, *J* = 7.2 Hz, C$\mathbf{H_2}CH_3$) 1.02-1.26 (3H, m, $C_6\mathbf{H}_{11}$), 0.82 (3H, t, *J* = 7.2 Hz, $CH_2C\mathbf{H_3}$), 0.75-0.97 (2H, m, $C_6\mathbf{H}_{11}$); ^{13}C NMR: δ 210.3, 169.1, 132.3, 128.6, 51.17, 47.63, 47.12, 34.14, 33.74, 33.15, 33.04, 26.08, 25.99, 23.45, 22.11, 13.56. LRMS (AP+) Calcd for $C_{17}H_{29}NO_2$ $(M + Na)^+$: 302.2, Found $(M + Na)^+$: 302.4.

Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material prepared by performing the diboration/imine allylation with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was determined by X-ray analysis of (*S*)-*N*-((*R*, *E*)-1-cyclohexyl-2-oxonon-5-en-4-yl)-2-methylbutanamide (**1.166**, see page 93), which was prepared by using (*S*)-(+)-2-methylbutyric anhydride (>99% ee) in place of Ac_2O in the protection step.

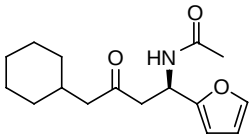
*Chiral HPLC (Chiralcel-OD-H, Daicel, 3.0 % iPrOH in hexanes, 0.9 mL/min) analysis of β-amidoketone product **1.158**:*



Racemic

Diboration-allylation-oxidation product

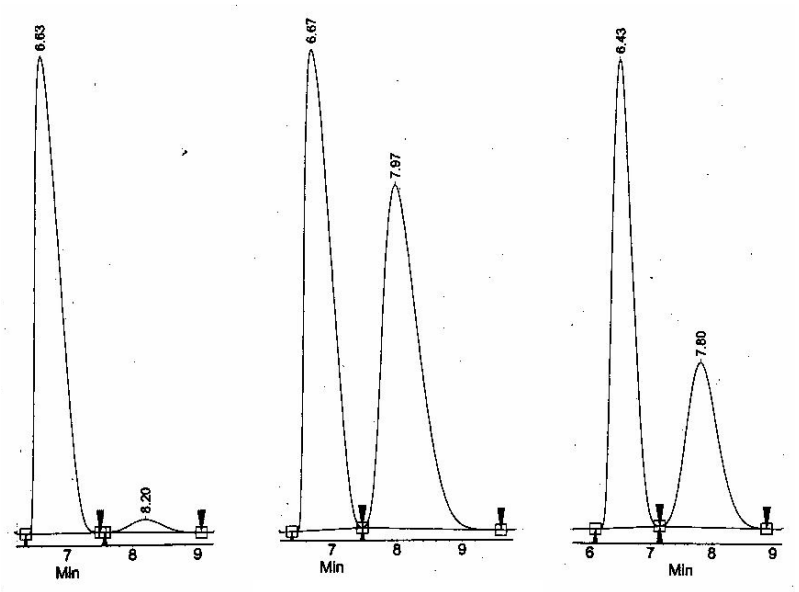
Diboration-allylation-oxidation product + racemic coinjection



(*R*)-*N*-(4-Cyclohexyl-1-(furan-2-yl)-3-oxobutyl)acetamide (1.159). The product was prepared according to the general allene diboration/imine allylation procedures on pages 57 and 60. A white solid. Mp 118-120 ^{o}C. R_f = 0.26 (4:1 CH_2Cl_2:Et_2O); IR (KBr): 3304 (br, s), 3064 (br, m), 2912 (br, s), 1693 (s), 1642 (s), 1537 (s), 1370 (s), 1285 (s) cm^{-1}; ^{1}H NMR: δ 7.25 (1H, s, Ar**H**), 6.68 (1H, d, *J* = 8.4 Hz, N**H**), 6.27 (1H, dd, *J* = 4.0 Hz, *J* = 2.6 Hz, Ar**H**), 6.12 (1H, d, *J* = 4.0 Hz, Ar**H**), 5.44 (1H, m, C**H**N), 3.06 (1H, dd, *J* = 17 Hz, *J* = 4.8 Hz, C(O)C**H$_a$**H$_b$CN), 2.80 (1H, dd, *J* = 17 Hz, *J* = 6.0 Hz, C(O)CH$_a$**H$_b$**CN), 2.23 (2H, d, *J* = 6.9 Hz, CyC**H$_2$**C(O)), 1.96 (3H, s, NC(O)C**H$_3$**), 1.50-1.85 (6H, m, C$_6$**H**$_{11}$), 1.0-1.35 (3H, m, C$_6$**H**$_{11}$), 0.75-1.0 (2H, m, C$_6$**H**$_{11}$); ^{13}C NMR: δ 209.3, 169.2, 153.4, 141.5, 110.4, 106.2, 50.95, 45.12, 43.83, 33.57, 33.02, 32.95, 26.04, 25.97, 23.22. LRMS (AP+) Calcd for $C_{16}H_{23}NO_3$ (M + Na)$^+$: 300.2, Found (M + Na)$^+$: 300.3.

Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material prepared by performing the diboration/imine allylation with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was assumed to be analogous to that obtained for (*R*)-*N*-(4-cyclohexyl-3-oxo-1-phenylbutyl)acetamide (**1.157**) and (*R,E*)-*N*-(1-cyclohexyl-2-oxonon-5-en-4-yl)acetamide (**1.158**).

*Chiral SFC (AS-H, Chiralpak, 150 bar, 50°C, flow = 3.0 mL/min, 3.0 % MeOH) analysis of β-amidoketone product **1.159**:*

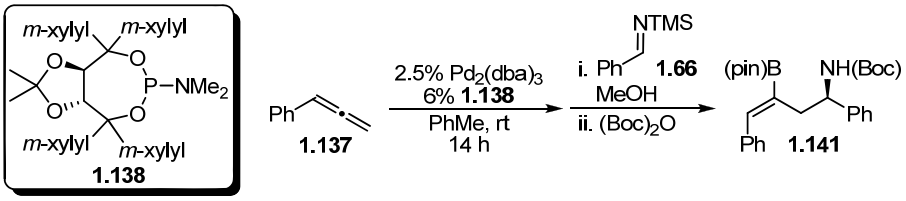


Diboration-allylation-oxidation product

Racemic

Diboration-allylation-oxidation product + racemic coinjection

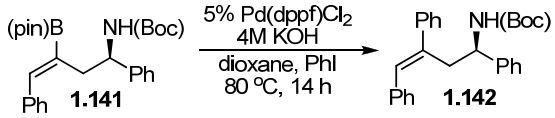
Synthesis of Vinylboronate Ester 1.141



The diboration-allylation sequence was carried out as described above when using silylaldimines (page 57) using 50.0 mg (0.430 mmol) of phenyl allene and 114 mg (0.645 mmol) of *N*-(trimethylsilyl)benzaldimine. After this was complete, 3.0 equiv of $(Boc)_2O$ was added, followed by 0.5 mL of $CHCl_3$. This mixture was allowed to stir for 1 h at ambient temperature. Volatile material was then removed under reduced pressure, and silica gel chromatography (hexanes/EtOAc) of the mixture afforded 114 mg (0.254 mmol, 59%) of **1.141** as a white foam.

(*R*,*Z*)-*tert*-Butyl-1,4-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enylcarbamate (1.141). R_f = 0.24 (CH_2Cl_2); IR (KBr): 3390 (br, m), 2975 (br, m), 1950 (w), 1717 (s), 1611 (m), 1514 (s), 1382 (s), 1344 (s), 1262 (s), 1165 (s) cm^{-1}; ^1H NMR: δ 7.41 (1H, s, vinyl C**H**), 7.12-7.38 (10H, m, Ar**H**), 5.81 (1H, br d, *J* = 5.2 Hz, N**H**), 4.71 (1H, br m, ArC**H**N), 2.77 (1H, m, C(B)C$\mathbf{H_a}H_b$CN), 2.54 (1H, m, C(B)C$H_a\mathbf{H_b}$CN), 1.37 (9H, s, OC(C$\mathbf{H_3}$)$_3$), 1.35 (6H, s, C(C$\mathbf{H_3}$)$_2$), 1.33 (6H, s, C(C$\mathbf{H_3}$)$_2$); ^{13}C NMR: δ 155.3, 145.7, 144.2, 137.3, 128.9, 128.3, 128.2, 127.5, 126.7, 125.8, 84.01, 78.86, 56.33, 36.48, 28.40, 24.98, 24.68. LRMS (ES+) Calcd for $C_{27}H_{36}BNO_4$ $(M + Na)^+$: 472.3, Found $(M + Na)^+$: 472.3.

Synthesis of Suzuki-Miyaura Coupling Product 1.142



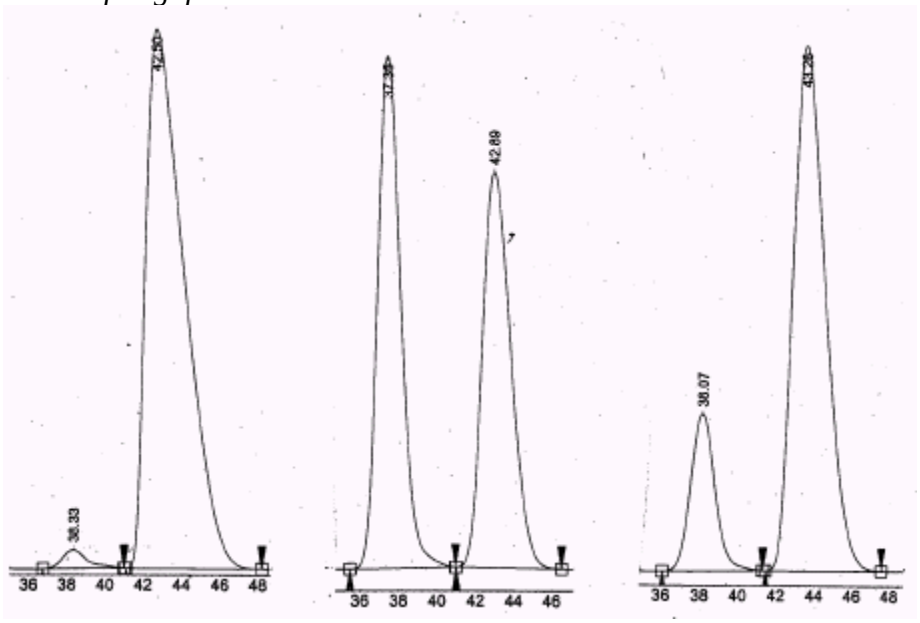
To 66.9 mg (0.149 mmol) of **1.141**, in a 20-mL scintillation vial with a magnetic stir-bar, was weighed 6.1 mg (0.0075 mmol) of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex. The vial was capped with a septum and purged with N_2. To the vial was added 1.06 mL of dioxane, followed by 25.1 μL (0.224 mmol) of iodobenzene, and lastly 0.11 mL of 4 M KOH. The septum was then quickly replaced with a polypropylene cap; the vial was sealed with electrical tape and heated at 80 ^{o}C for 14 h. After this time period, the mixture was transferred to a separatory funnel with 20 mL of CH_2Cl_2 and 10 mL of H_2O. The organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (1 x 20 mL). The combined organics were washed with 15 mL of H_2O, 10 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel chromatography (9:1 hexanes:EtOAc) afforded 37.2 mg (0.0931 mmol, 62 %) of (*R*,*E*)-*tert*-butyl-1,3,4-triphenylbut-3-enylcarbamate (**1.142**) as a waxy solid.

(*R*,*E*)-*tert*-Butyl-1,3,4-triphenylbut-3-enylcarbamate (1.142). R_f = 0.18 (9:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3437 (br, m), 2966 (br, m), 1953 (w), 1705 (s), 1495 (s), 1363 (s), 1246 (m), 1165 (s) cm^{-1}; ^{1}H NMR: δ 7.45 (2H, d, *J* = 7.2 Hz, Ar**H**), 7.40 (2H, t, *J* = 7.2 Hz, Ar**H**), 7.33 (3H, t, *J* = 7.6 Hz, Ar**H**), 7.17-7.29 (4H, m, Ar**H**), 7.11 (2H, d, *J* = 7.6 Hz, Ar**H**), 7.00 (2H, dd, *J* = 7.6 Hz, *J* = 2.0 Hz, Ar**H**), 6.75 (1H, s,

vinyl C**H**), 4.65 (2H, br s, N**H** + ArC**H**N), 3.19 (1H, m, ArCHNC$\mathbf{H_a}H_b$), 3.07 (1H, m, ArCHNC$H_a\mathbf{H_b}$), 1.37 (9H, s, OC(C$\mathbf{H_3}$)$_3$); ^{13}C NMR: δ 154.8, 142.1, 139.4, 137.7, 131.2, 128.8, 128.5, 128.3, 128.2, 127.4, 127.1, 126.8, 126.7, 126.2, 53.85, 37.26, 28.28. LRMS (ES+) Calcd for $C_{27}H_{29}NO_2$ (M + Na)$^+$: 422.2, Found (M + Na)$^+$: 422.4.

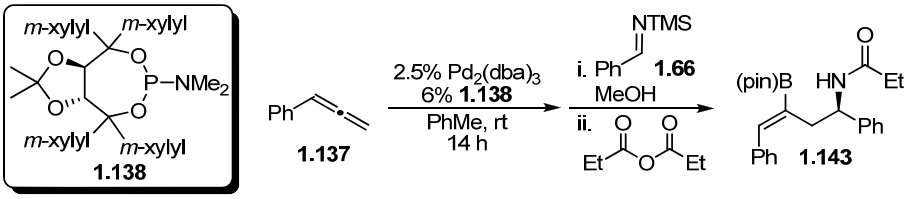
Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material, which was prepared using racemic starting material that had been synthesized as described above with tricyclohexylphosphine in place of the chiral ligand in the diboration step. Absolute configuration was assumed to be analogous to that obtained for (*R*)-*N*-(3-oxo-1,4-diphenylbutyl)acetamide (**1.136**).

*Chiral SFC (AD-H, Chiralpak, 150 bar, 50^{o}C, flow = 0.5 mL/min, 5.0 % MeOH) analysis of the Suzuki-coupling product **1.142**:*



Suzuki product | Racemic | Suzuki product + racemic coinjection

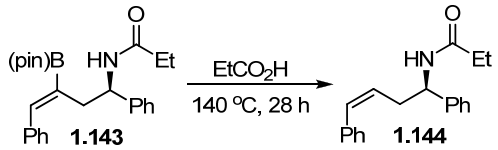
Synthesis of Vinylboronate Ester 1.143



The diboration-allylation sequence was carried out as described above when using silylaldimines (page 57) using 50.0 mg (0.430 mmol) of phenyl allene and 114 mg (0.645 mmol) of *N*-(trimethylsilyl)benzaldimine. After this was complete, 3.0 equiv of the propionic anhydride was added, followed by 0.5 mL of $CHCl_3$. This mixture was allowed to stir for 1 h at ambient temperature. Volatile material was then removed under reduced pressure, and silica gel chromatography (hexanes/EtOAc) of the mixture afforded 108 mg (0.266 mmol, 62%) of **1.143** as a waxy solid.

(*R,Z*)-*N*-(1,4-Diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl)propionamide (1.143). R_f = 0.27 (10:1 CH_2Cl_2:Et_2O); IR (KBr): 3293 (br, s), 3060 (br, m), 2970 (br, m), 1949 (w), 1642 (s), 1600 (s), 1537 (s), 1355 (s), 1142 (s) cm^{-1}; ^1H NMR: δ 7.10-7.48 (11H, m, Ar**H** + vinyl C**H**), 6.36 (1H, d, *J* = 6.8 Hz, N**H**), 5.05 (1H, m, ArC**H**N), 2.82 (1H, m, C(B)C$\mathbf{H_a}H_b$CN), 2.73 (1H, m, C(B)C$H_a\mathbf{H_b}$CN), 2.12 (2H, q, *J* = 7.6 Hz, NC(O)C$\mathbf{H_2}$CH$_3$), 1.32 (6H, s, C(C$\mathbf{H_3}$)$_2$), 1.30 (6H, s, C(C$\mathbf{H_3}$)$_2$), 1.08 (3H, t, *J* = 7.6 Hz, NC(O)CH$_2$C$\mathbf{H_3}$); ^{13}C NMR: δ 172.9, 145.9, 143.2, 137.3, 128.9, 128.33, 128.31, 127.5, 126.8, 126.0, 83.94, 54.33, 35.87, 29.63, 25.18, 24.51, 9.78. LRMS (AP+) Calcd for $C_{25}H_{32}BNO_3$ $(M + Na)^+$: 428.2, Found $(M + Na)^+$: 428.5.

Synthesis of Protonation Product 1.144



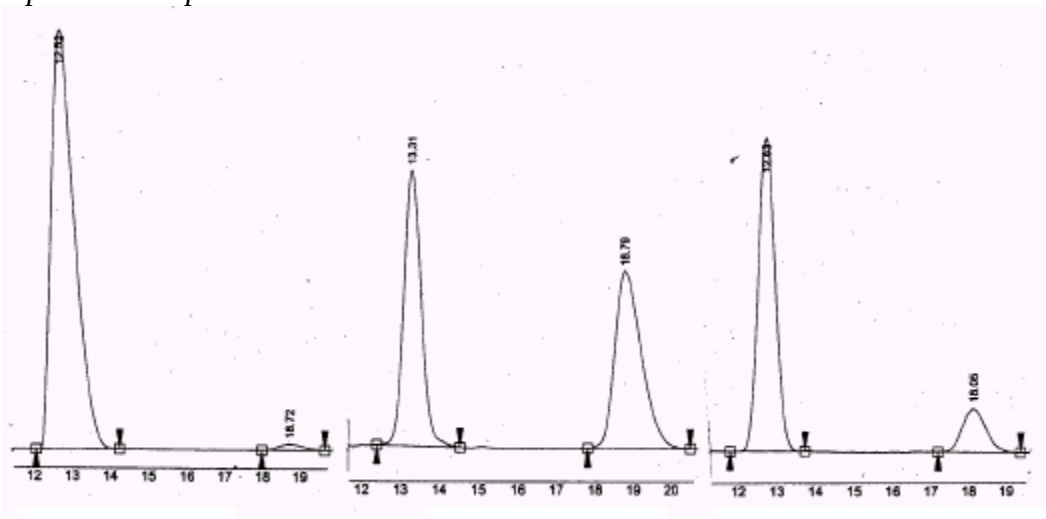
To 85.2 mg (0.210 mmol) of **1.143**, in a 20-mL scintillation vial with a magnetic stir-bar, was added 2.1 mL of propionic acid. The vial was purged with N_2, capped with a polypropylene cap, sealed with electrical tape, and heated at 140 ^oC for 28 h. After this time period, the mixture was transferred to a separatory funnel with 20 mL of Et_2O and extracted with saturated aqueous $NaHCO_3$ (3 x 15 mL). The combined aqueous layers were then extracted with Et_2O (1 x 20 mL). The combined organics were washed with 10 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a brown solid. Purification using silica gel chromatography (20:1 CH_2Cl_2:Et_2O) afforded 54.2 mg (0.194 mmol, 92 %) of (*R,Z*)-*N*-(1,4-diphenylbut-3-enyl)propionamide (**1.144**) as a white solid.

(*R,Z*)-*N*-(1,4-Diphenylbut-3-enyl)propionamide (1.144). R_f = 0.22 (20:1 CH_2Cl_2:Et_2O); IR (KBr): 3328 (br, m), 3017 (br, m), 2940 (br, m), 1953 (w), 1884 (w), 1802 (w), 1642 (s), 1530 (s), 1452 (s), 1383 (s), 1274 (s), 1102 (s) cm^{-1}; ^1H NMR: δ 7.15-7.39 (10H, m, Ar**H**), 6.51 (1H, d, *J* = 11.6 Hz, ArC**H**=CH), 5.71 (1H, d, *J* = 8.0 Hz, N**H**), 5.58 (1H, m, ArCH=C**H**CH_2), 5.13 (1H, q, *J* = 7.6 Hz, ArC**H**N), 2.84 (2H, t, *J* = 6.8 Hz, ArCH=CHC**H_2**), 2.15 (2H, q, *J* = 7.6 Hz, C**H_2**CH_3), 1.10 (3H, t, *J* = 7.6 Hz, CH_2C**H_3**); ^{13}C NMR: δ 173.0, 141.63, 137.0, 131.5, 128.7, 128.6, 128.3, 127.7, 127.4,

126.9, 126.5, 52.97, 34.93, 29.69, 9.76. LRMS (ES+) Calcd for $C_{19}H_{21}NO$ $(M + Na)^+$: 302.2, Found $(M + Na)^+$: 302.3.

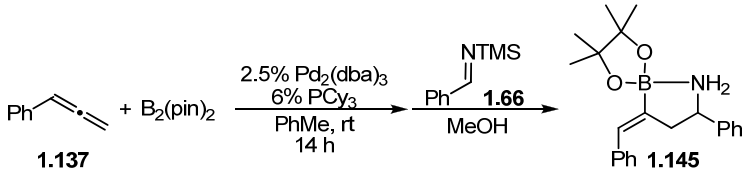
Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material, which was prepared using racemic starting material that had been synthesized as described above with tricyclohexylphosphine in place of the chiral ligand in the diboration step. Absolute configuration was assumed to be analogous to that obtained for (*R*)-*N*-(3-oxo-1,4-diphenylbutyl)acetamide (**1.136**).

*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 4.0 mL/min, 3.0 % MeOH) analysis of the protonation product **1.144**:*



Protonation product | Racemic | Protonation product + racemic coinjection

Synthesis of Aminoboronate 1.145

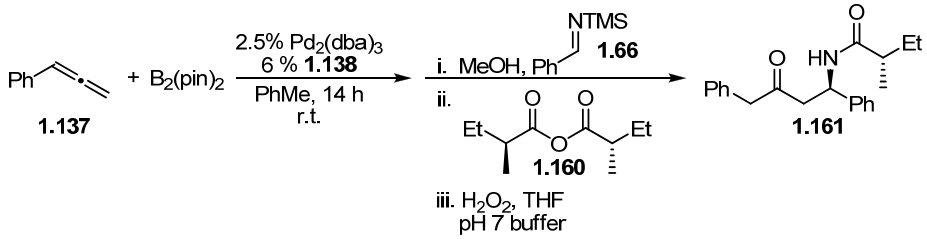


An oven-dried 2-dram vial equipped with a magnetic stir-bar was charged with 9.9 mg (0.011 mmol) of tris(dibenzylideneacetone)dipalladium(0), 7.2 mg (0.0258 mmol) of PCy_3, and 2.7 mL of toluene in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min; then, 131 mg (0.516 mmol) of bis(pinacolato)diboron was added followed by 50.0 mg (0.430 mmol) of phenyl allene. The vial was capped, sealed with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 14 h. After this time period, the vial was taken back into the dry-box, and 76.2 mg (0.430 mmol) of *N*-(trimethylsilyl)benzaldimine was weighed in. Next, 20.9 μL (0.516 mmol) of MeOH was added dropwise while stirring the reaction. A white precipitate formed after 1h at ambient temperature, and the mixture was then poured into 15 mL of hexanes. The mixture was filtered using vacuum filtration, and 55 mg (0.16 mmol, 37%) of an off-white solid was collected. Recrystallization from a mixture of hexanes and EtOAc afforded X-ray quality crystals. See page 95 for crystal parameters.

(*Z*)-1,4-Diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-amine (1.145). Mp 170-173 ^{o}C. IR (KBr): 3309 (br, m), 3196 (br, m), 3067 (br, s), 2971 (br, s), 1945 (w), 1884 (w), 1806 (w), 1596 (s), 1495 (s), 1460 (s), 1383 (s), 1212 (s), 1150 (s)

cm^{-1}; ^1H NMR: δ 7.24-7.50 (5H, m, Ar**H**), 7.11 (5H, s, ArC**H**), 6.85 (1H, s, vinyl C**H**), 3.5-5.0 (2H, br s, N$\mathbf{H_2}$), 4.09 (1H, m, ArC**H**N), 2.93 (1H, m, ArCH(N)C$\mathbf{H_a}H_b$), 2.83 (1H, m, ArCH(N)C$H_a\mathbf{H_b}$), 1.20 (6H, s, C(C$\mathbf{H_3}$)$_2$), 1.17 (6H, s, C(C$\mathbf{H_3}$)$_2$); ^{13}C NMR: δ 140.9, 139.3, 131.6, 128.7, 128.6, 128.1, 127.9, 126.9, 125.9, 80.25, 57.26, 38.84, 25.49. LRMS (ES+) Calcd for $C_{22}H_{28}BNO_2$ $(M + H)^+$: 350.2, Found $(M + H)^+$: 350.4.

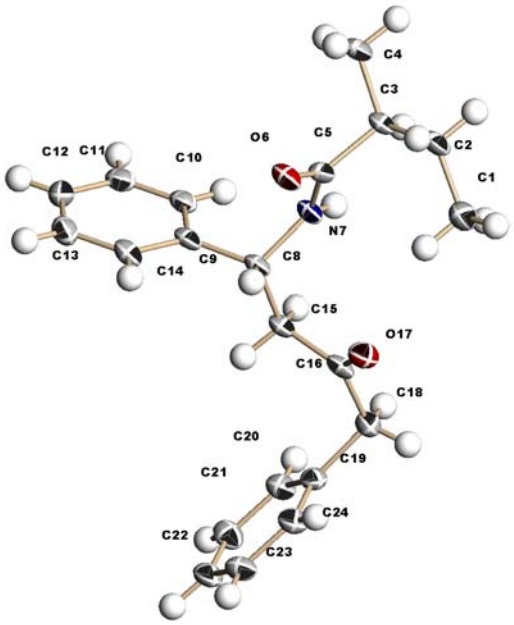
Procedure for Absolute Stereochemistry Determination of 1.136 by X-ray Analysis



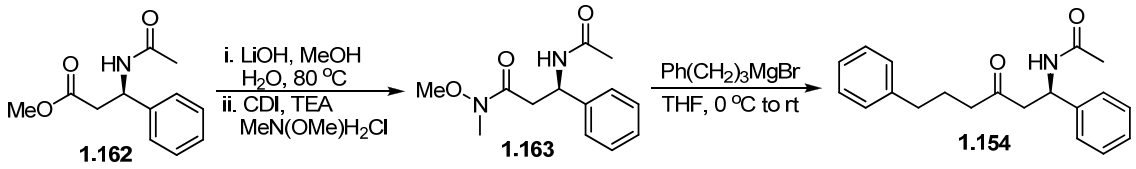
The diboration/allylation was carried out as described above when using silylaldimines using 69.7 mg (0.600 mmol) of phenyl allene and 70.8 mg (0.400 mmol) of *N*-(trimethylsilyl)benzaldimine (**1.66**). After the allylation step was complete, 0.24 mL (1.2 mmol) of (*S*)-(+)-2-methylbutyric anhydride (**1.160**, >98% ee and commercially available from Aldrich Chemical Co.) was added in place of Ac_2O in the dry-box. After oxidation and the aqueous workup, silica gel column chromatography (30:1 CH_2Cl_2:Et_2O) afforded 71 mg (0.33 mmol, 55%) of (*S*)-2-methyl-*N*-((*R*)-3-oxo-1,4-diphenylbutyl)butanamide (**1.161**) as a white solid. Recrystallization using a mixture of hexanes and EtOAc afforded X-ray quality crystals.

(*S*)-2-Methyl-*N*-[(*R*)-3-oxo-1,4-diphenylbutyl]butanamide (1.161). Mp 115-118 ^{o}C. R_f = 0.19 (2:1 hexanes:EtOAc); IR (KBr): 3328 (br, m), 3029 (br, m), 2928 (br, m), 1945 (w), 1871 (w), 1706 (s), 1639 (s), 1526 (s), 1491 (s), 1449 (s), 1238 (s), 1172 (s) cm^{-1}; ^{1}H NMR: δ 7.20-7.32 (6H, m, Ar**H**), 7.16 (2H, d, *J* = 7.2 Hz, Ar**H**), 7.04 (2H, d, *J* = 6.8 Hz, Ar**H**), 6.57 (1H, d, *J* = 7.6 Hz, N**H**), 5.40 (1H, m, ArC**H**N), 3.62 (1H, d, *J* = 16 Hz, ArC**H$_a$**H$_b$C(O)), 3.56 (1H, d, *J* = 16 Hz, ArCH$_a$**H$_b$**C(O)), 3.10 (1H, dd, *J* = 16 Hz, *J* = 5.6 Hz, C(O)C**H$_a$**H$_b$CN), 2.89 (1H, dd, *J* = 16 Hz, *J* = 6.0 Hz, C(O)CH$_a$**H$_b$**CN), 2.09 (1H, h, *J* = 7.2 Hz, NC(O)C**H**), 1.63 (1H, m, NC(O)CHC**H$_a$**H$_b$CH$_3$), 1.40 (1H, m, NC(O)CHCH$_a$**H$_b$**CH$_3$), 1.08 (3H, d, *J* = 6.8 Hz, CHC**H$_3$**), 0.86 (3H, t, *J* = 7.6 Hz, CH$_2$C**H$_3$**); ^{13}C NMR: δ 207.2, 175.7, 140.9, 133.3, 129.4, 128.7, 128.6, 127.3, 127.1, 126.1, 50.69, 49.13, 46.47, 43.07, 27.18, 17.30, 11.82. LRMS (ES+) Calcd for $C_{21}H_{25}NO_2$ (M + Na)$^{+}$: 346.2, Found (M + Na)$^{+}$: 346.3.

Figure 1.6: Crystal Structure of 1.161



Procedure for Absolute Stereochemistry Determination of 1.154



A 50 mL RBF with magnetic stir-bar was charged with 445 mg (10.6 mmol) of $LiOH{\cdot}H_2O$, followed by 1.17 g (5.29 mmol) of **1.162**,[61] and lastly 12.6 mL of a 3:1 MeOH:H_2O mixture. The flask was purged with N_2, fitted with a reflux condenser, and heated at 80 °C for 1 h. After cooling to room temperature, the reaction was acidified with 40 mL of 1 M HCl and extracted with EtOAc (2x, ~50 mL). The combined organics were dried with anhydrous Na_2SO_4 and concentrated into a 100 mL RBF. A magnetic stir-bar was added, and the flask purged with N_2. Next, 36 mL of CH_2Cl_2 was added by syringe, and the mixture was cooled to 0 °C. 1.12 g (6.88 mmol) of CDI was added, the ice bath was removed, and the reaction was allowed to stir at ambient temperature for 30 min. The mixture was recooled to 0 °C and 671 mg (6.88 mmol) of (*N*,*O*)-dimethylhydroxylamine hydrochloride was added, followed by 0.96 mL (6.9 mmol) of TEA. The ice bath was removed, and the mixture was allowed to stir at ambient temperature for 24 h. Next, 3.5 mL of Ac_2O was added and stirring was continued for an additional 1 h. The reaction was transferred to a separatory funnel and washed sequentially with saturated aqueous $NaHCO_3$ (2x), 1 M HCl (2x), and brine (1x). The organic layer was dried with anhydrous Na_2SO_4, and volatile material was removed under

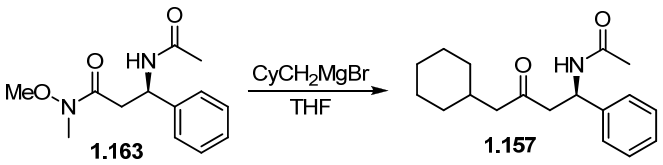
[61] **1.162** was prepared in 52% yield and 18% ee using (*R*)-BINAP according to reference 58.

reduced pressure. Purification of the mixture using silica gel chromatography (5% MeOH in EtOAc) afforded 873 mg (3.49 mmol, 66%) of **1.163** as a white solid.

(*R*)-3-Acetamido-*N*-methoxy-*N*-methyl-3-phenylpropanamide (1.163). R_f = 0.19 (5% MeOH in EtOAc); IR (KBr): 3352 (br, s), 3033 (br, m), 2940 (br, m), 1957 (w), 1876 (w), 1670 (s), 1631 (s), 1534 (s), 1460 (s), 1367 (s), 1293 (s), 1204 (s) cm^{-1}; ^1H NMR: δ 7.41 (1H, d, *J* = 6.8 Hz, N**H**), 7.15-7.40 (5H, m, Ar**H**), 5.39 (1H, m, ArC**H**N), 3.44 (3H, s, C$\mathbf{H_3}$), 3.12 (1H, dd, *J* = 16 Hz, *J* = 5.0 Hz, ArCH(N)C$\mathbf{H_a}H_b$), 3.06 (3H, s, C$\mathbf{H_3}$), 2.77 (1H, dd, *J* = 16 Hz, *J* = 5.0 Hz, ArCH(N)C$H_a\mathbf{H_b}$), 1.99 (3H, s, NC(O)C$\mathbf{H_3}$); ^{13}C NMR: δ 171.9, 169.3, 141.3, 128.5, 127.2, 126.2, 61.16, 49.66, 36.65, 31.73, 23.36. LRMS (ES+) Calcd for $C_{13}H_{18}N_2O_3$ $(M + Na)^+$: 273.1, Found $(M + Na)^+$: 273.2.

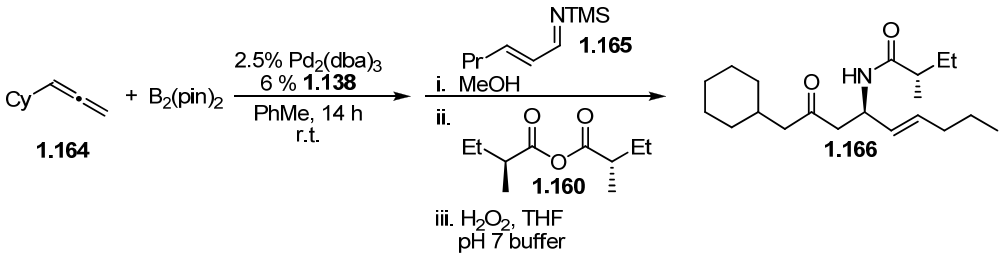
To 38.1 mg (0.152 mmol) of **1.163** in 1.5 mL of THF at 0 ^oC was added 0.60 mL of a 0.78 M solution of (3-phenylpropyl)magnesium bromide in THF dropwise. This mixture was allowed to stir for 2 h at 0 ^oC and then, at ambient temperature for 20 min. The reaction was quenched by the addition of 3 mL of saturated aqueous NH_4Cl. Water was added, and the mixture extracted with CH_2Cl_2. The combined organics were washed with 1 M HCl (2x), brine, and dried with anhydrous Na_2SO_4. After removal of volatile material under reduced pressure, silica gel chromatography (hexanes/EtOAc) of the mixture afforded 21.1 mg (0.0682 mmol, 45%) of **1.154**. Spectral data were in good agreement with **1.154** prepared by the tandem diboration/allylation sequence.

Procedure for Absolute Stereochemistry Determination of 1.157



To 48.0 mg (0.192 mmol) of **1.163** in 1.9 mL of THF at 0 ^{o}C was added 0.89 mL of a 0.67 M solution of (cyclohexylmethyl)magnesium bromide in THF dropwise. This mixture allowed to reach ambient temperature and allowed to stir overnight. The reaction was quenched by the addition of 3 mL of saturated aqueous NH_4Cl. Water was added, and the mixture extracted with CH_2Cl_2. The combined organics were washed with 1 M HCl (2x), brine, and dried with anhydrous Na_2SO_4. After removal of volatile material under reduced pressure, silica gel chromatography (hexanes/EtOAc) of the mixture afforded 3.3 mg (0.012 mmol, 6%) of **1.157**. Spectral data were in good agreement with **1.157** prepared by the tandem diboration/allylation sequence.

Procedure for Absolute Stereochemistry Determination of 1.158 by X-ray Analysis

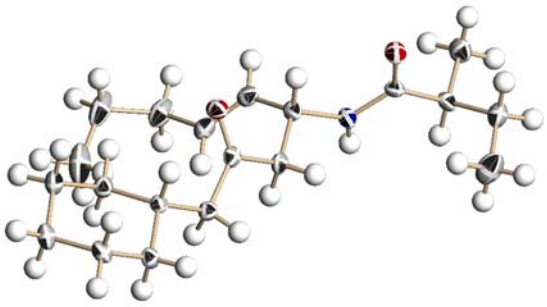


The diboration/allylation was carried out as described above when using silylaldimines (page 57) using 50.0 mg (0.409 mmol) of cyclohexyl allene and 104 mg (0.614 mmol) of silylaldimine **1.165**. After the allylation step was complete, 0.24 mL (1.2 mmol) of (*S*)-(+)-2-methylbutyric anhydride (**1.160**, >98% ee and commercially available from Aldrich Chemical Co.) was added in place of Ac_2O in the dry-box. After oxidation and the aqueous workup, silica gel column chromatography (30:1 CH_2Cl_2:Et_2O) afforded 81.7 mg (0.254 mmol, 62 %) of (*S*)-*N*-((*R*, *E*)-1-cyclohexyl-2-oxonon-5-en-4-yl)-2-methylbutanamide (**1.166**) as a white solid. Recrystallization using a mixture of hexanes and EtOAc afforded X-ray quality crystals.

(*S*)-*N*-[(*R*,*E*)-1-Cyclohexyl-2-oxonon-5-en-4-yl]-2-methylbutanamide (1.166). Mp 92-96 ^{o}C. R_f = 0.19 (30:1 CH_2Cl_2:Et_2O); IR (KBr): 3393 (br, s), 2916 (br, s), 1709 (s), 1631 (s), 1538 (s), 1383 (m), 1281 (m) cm^{-1}; ^{1}H NMR: δ 6.26 (1H, d, *J* = 8.4 Hz, N**H**), 5.52 (1H, dt, *J* = 16 Hz, *J* = 6.4 Hz, vinyl), 5.43 (1H, dd, *J* = 16 Hz, *J* = 6.0 Hz, vinyl), 4.70 (1H, m, CH=CHC**H**N), 2.73 (1H, dd, *J* = 17 Hz, *J* = 4.8 Hz, C(O)C$\mathbf{H_a}$$H_b$CN), 2.63 (1H, dd, *J* = 17 Hz, *J* = 5.6 Hz, C(O)$CH_a$$\mathbf{H_b}$CN), 2.23 (2H, d, *J* = 6.8 Hz, CyC$\mathbf{H_2}$C(O)), 2.04 (1H, h, *J* = 6.8 Hz, NC(O)C**H**(CH_3)CH_2-), 1.93 (2H, q, *J* = 7.2 Hz, allylic C$\mathbf{H_2}$), 1.54-

1.86 (7H, m, aliphatic), 1.03-1.45 (7H, m, aliphatic), 1.07 (3H, d, *J* = 6.8 Hz, NC(O)CH(C**H**$_3$)CH$_2$-), 0.77-0.96 (7H, m, aliphatic); ^{13}C NMR: δ 210.3, 175.4, 132.2, 128.8, 51.15, 47.30, 47.26, 43.19, 34.16, 33.78, 33.15, 33.06, 27.25, 26.10, 26.00, 21.15, 17.35, 13.54, 11.81. LRMS (ES+) Calcd for $C_{20}H_{35}NO_2$ $(M + Na)^+$: 344.3, Found $(M + Na)^+$: 344.2.

Figure 1.7: Crystal Structure of 1.166



X-ray Data for 1.145

Space Group and Cell Dimensions Monoclinic, P $2_1/c$
a 12.6666(10) b 19.3167(15) c 8.4376(6)
beta 105.406(6)
Volume 1990.3(3)A**3

Empirical formula : C22 H28 B N O2

Cell dimensions were obtained from 732 reflections with 2Theta angle in the range 5.00 - 50.00 degrees.

Crystal dimensions : 0.30 X 0.02 X 0.02 mm

FW = 349.28 Z = 4 F(000) = 752.40

Dcalc 1.166Mg.m-3, mu 0.07mm-1, lambda 0.71073A, 2Theta(max) 50.0

The intensity data were collected on a Bruker SMART 1K diffractometer, using the omega scan mode.
The h,k,l ranges used during structure solution and refinement are :--Hmin,max -15 14; Kmin,max 0 22; Lmin,max 0 10

No. of reflections measured	11886
No. of unique reflections	3494
No. of reflections with Inet > 2.5sigma(Inet)	1595

Merging R-value on intensities 0.037
Correction was made for absorption using SADABS

Details of the last least squares cycle
54 atoms, 235 parameters Full-matrix on Fo Counter wts (k 0.000400)

The residuals are as follows :--

Significant reflections:	1590	Rf 0.071,	Rw 0.072
All reflections:	3494	Rf 0.161,	Rw 0.084
Included reflections:	1590	Rf 0.071,	Rw 0.072
			GoF 2.0295

where Rf = Sum(Fo-Fc)/Sum(Fo),
Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]

The maximum shift/sigma ratio was 0.000.

Last D-map: Minimum density -0.310e/A**3,
Maximum density 0.430e/A**3.

Table 1. Atomic Parameters x,y,z and Biso.
E.S.Ds. refer to the last digit printed.

	x	y	z	Biso
B1	0.8037 (5)	0.2052 (3)	0.1942(7)	3.2 (3)
O2	0.85974(25)	0.17727(15)	0.0785(3)	3.30(15)
C3	0.9617 (4)	0.1482 (3)	0.1705(6)	3.9 (3)
C4	1.0499 (4)	0.2050 (3)	0.2071(7)	5.9 (3)
C5	0.9978 (5)	0.0926 (3)	0.0699(7)	5.9 (3)
C6	0.9361 (4)	0.1241 (3)	0.3282(6)	4.2 (3)
C7	1.0314 (5)	0.1169 (3)	0.4767(7)	6.3 (3)
C8	0.8732 (5)	0.0546 (3)	0.3015(7)	6.4 (4)
O9	0.8622 (3)	0.17714(16)	0.3539(3)	4.13(17)
C10	0.6724 (4)	0.2050 (3)	0.1409(5)	3.4 (3)
C11	0.6053 (4)	0.1512 (3)	0.0922(5)	3.4 (3)
C12	0.4856 (5)	0.1509 (3)	0.0330(6)	3.6 (3)
C13	0.4335 (5)	0.1100 (3)	-0.1000(7)	4.9 (3)
C14	0.3213 (6)	0.1123 (4)	-0.1668(7)	6.3 (4)
C15	0.2579 (5)	0.1555 (4)	-0.1006(10)	6.6 (4)
C16	0.3067 (6)	0.1946 (3)	0.0340(9)	5.9 (4)
C17	0.4180 (5)	0.1930 (3)	0.1006(7)	5.0 (3)
C18	0.6312 (4)	0.2789 (3)	0.1418(7)	5.8 (3)
C19	0.7165 (5)	0.3237 (3)	0.1198(7)	5.8 (3)
C20	0.7019 (4)	0.4005 (3)	0.1391(6)	3.9 (3)
C21	0.7276 (4)	0.4332 (3)	0.2881(6)	4.3 (3)
C22	0.7101 (5)	0.5028 (4)	0.3003(8)	5.9 (4)
C23	0.6637 (6)	0.5404 (3)	0.1660(11)	6.8 (5)
C24	0.6347 (6)	0.5096 (4)	0.0181(9)	8.1 (5)
C25	0.6533 (6)	0.4391 (4)	0.0022(7)	7.0 (4)
N26	0.8204 (3)	0.29206(19)	0.2056(4)	3.65(20)
H4a	1.049	0.229	0.107	6.8
H4b	1.121	0.185	0.251	6.8
H4c	1.035	0.237	0.285	6.8
H5a	0.941	0.058	0.039	6.7
H5b	1.064	0.071	0.134	6.7
H5c	1.011	0.113	-0.027	6.7
H7a	1.067	0.161	0.502	6.8
H7b	1.082	0.084	0.455	6.8

H7c	1.006	0.102	0.569	6.8
H8a	0.846	0.045	0.395	7.2
H8b	0.922	0.018	0.289	7.2
H8c	0.813	0.057	0.205	7.2
H11	0.640	0.107	0.097	4.2
H13	0.476	0.079	-0.146	5.8
H14	0.288	0.084	-0.260	7.0
H15	0.180	0.158	-0.148	7.4
H16	0.262	0.224	0.082	7.0
H17	0.450	0.221	0.195	6.1
H18a	0.564	0.285	0.058	6.9
H18b	0.619	0.289	0.247	6.9
H19	0.713	0.318	0.005	6.4
H21	0.760	0.407	0.386	5.2
H22	0.731	0.525	0.406	6.7
H23	0.651	0.589	0.175	7.9
H24	0.600	0.536	-0.078	9.3
H25	0.634	0.418	-0.104	7.9
H26a	0.839	0.307	0.318	4.6
H26b	0.878	0.306	0.158	4.6

Biso is the Mean of the Principal Axes of the Thermal Ellipsoid

Table of u(i,j) or U values *100.
E.S.Ds. refer to the last digit printed

	u11(U)	u22	u33	u12	u13	u23
B1	5.3(4)	3.2(4)	3.7(3)	0.0(3)	1.4(3)	0.2(3)
O2	4.89(22)	4.01(21)	4.10(18)	1.38(17)	2.00(17)	0.46(16)
C3	4.4(4)	5.0(4)	5.5(3)	1.4(3)	1.5(3)	0.3(3)
C4	6.3(4)	6.3(4)	10.1(5)	1.0(3)	2.9(4)	1.1(4)
C5	7.4(4)	6.6(4)	8.3(4)	3.1(3)	2.0(3)	-0.5(3)
C6	6.6(4)	4.0(4)	4.7(3)	1.9(3)	0.4(3)	0.7(3)
C7	10.0(5)	5.7(4)	7.4(4)	1.5(4)	0.7(4)	1.2(3)
C8	9.1(5)	4.7(4)	10.6(5)	0.9(3)	3.1(4)	1.8(3)
O9	7.2(3)	4.50(23)	4.32(20)	1.65(20)	2.17(18)	0.83(17)
C10	5.2(4)	3.4(3)	5.1(3)	0.6(3)	2.5(3)	0.7(3)
C11	4.8(4)	4.2(3)	3.9(3)	0.6(3)	1.3(3)	0.15(25)
C12	5.1(4)	5.0(4)	4.2(3)	-0.4(3)	2.1(3)	0.3(3)
C13	5.2(5)	7.6(5)	6.4(4)	-0.4(3)	2.2(3)	-1.1(3)
C14	6.1(5)	9.4(6)	8.0(4)	-0.9(4)	1.2(4)	-1.3(4)

C15	5.2(5)	8.7(6)	11.1(6)	-0.3(4)	2.2(4)	1.0(5)
C16	5.6(5)	7.3(5)	10.8(5)	0.5(4)	4.2(4)	0.0(4)
C17	6.1(4)	5.8(4)	8.2(4)	-0.5(3)	4.1(4)	-0.9(3)
C18	5.8(4)	4.8(4)	12.4(5)	1.3(3)	4.4(4)	2.0(4)
C19	7.4(5)	4.4(4)	9.5(5)	1.7(4)	1.0(4)	-0.1(3)
C20	6.3(4)	4.0(4)	5.2(4)	1.1(3)	2.6(3)	-0.2(3)
C21	6.7(4)	4.2(4)	5.7(4)	-0.2(3)	2.2(3)	0.4(3)
C22	8.1(5)	5.4(5)	9.0(5)	0.0(4)	2.7(4)	-1.9(4)
C23	9.5(6)	4.3(5)	13.4(7)	1.2(4)	5.5(5)	0.2(5)
C24	15.3(7)	7.5(6)	9.7(6)	6.5(5)	6.1(5)	4.7(5)
C25	13.6(6)	9.1(5)	4.4(4)	5.0(5)	3.0(4)	0.0(4)
N26	4.5(3)	3.7(3)	6.2(3)	0.95(21)	2.32(22)	0.43(21)
H4a	8.6					
H4b	8.6					
H4c	8.6					
H5a	8.4					
H5b	8.4					
H5c	8.4					
H7a	8.7					
H7b	8.7					
H7c	8.7					
H8a	9.1					
H8b	9.1					
H8c	9.1					
H11	5.3					
H13	7.4					
H14	8.8					
H15	9.4					
H16	8.9					
H17	7.7					
H18a	8.7					
H18b	8.7					
H19	8.1					
H21	6.6					
H22	8.5					
H23	10.1					
H24	11.8					
H25	10.0					
H26a	5.8					
H26b	5.8					

Anisotropic Temperature Factors are of the form
Temp=-2*Pi*Pi*(h*h*u11*astar*astar+---

+2*h*k*u12*astar*bstar+---)

DISANG -- The NRCVAX Distance and Angle Program

The Space Group is P 21/C Centrosymmetric
The Equivalent Positions are:
1) x y z 2) -x 1/2+y 1/2-z

The Lattice is Primitive. There are no Centering Vectors

Bond lengths (Å):

B(1)-O(2)	1.454(6)	C(12)-C(17)	1.407(8)
B(1)-O(9)	1.459(6)	C(13)-C(14)	1.384(9)
B(1)-C(10)	1.604(8)	C(14)-C(15)	1.375(11)
B(1)-N(26)	1.691(7)	C(15)-C(16)	1.366(12)
O(2)-C(3)	1.433(6)	C(16)-C(17)	1.372(10)
C(3)-C(4)	1.537(8)	C(18)-C(19)	1.435(9)
C(3)-C(5)	1.513(7)	C(19)-C(20)	1.508(8)
C(3)-C(6)	1.524(7)	C(19)-N(26)	1.458(7)
C(6)-C(7)	1.498(8)	C(20)-C(21)	1.367(8)
C(6)-C(8)	1.547(8)	C(20)-C(25)	1.374(8)
C(6)-O(9)	1.442(6)	C(21)-C(22)	1.370(9)
C(10)-C(11)	1.337(8)	C(22)-C(23)	1.344(12)
C(10)-C(18)	1.520(7)	C(23)-C(24)	1.343(13)
C(11)-C(12)	1.465(8)	C(24)-C(25)	1.395(11)
C(12)-C(13)	1.389(8)		

Bond angles (deg):

O(2)-B(1)-O(9)	105.3(4)	C(10)-C(11)-C(12)	128.6(4)
O(2)-B(1)-C(10)	117.8(4)	C(11)-C(12)-C(13)	120.3(5)
O(2)-B(1)-N(26)	109.3(4)	C(11)-C(12)-C(17)	123.1(5)
O(9)-B(1)-C(10)	119.5(4)	C(13)-C(12)-C(17)	116.6(5)
O(9)-B(1)-N(26)	106.9(4)	C(12)-C(13)-C(14)	121.8(5)
C(10)-B(1)-N(26)	97.0(4)	C(13)-C(14)-C(15)	120.1(6)
B(1)-O(2)-C(3)	108.2(3)	C(14)-C(15)-C(16)	119.2(6)
O(2)-C(3)-C(4)	109.3(4)	C(15)-C(16)-C(17)	121.2(6)
O(2)-C(3)-C(5)	109.7(4)	C(12)-C(17)-C(16)	121.1(5)
O(2)-C(3)-C(6)	102.8(4)	C(10)-C(18)-C(19)	107.2(4)
C(4)-C(3)-C(5)	107.9(4)	C(18)-C(19)-C(20)	117.5(5)
C(4)-C(3)-C(6)	110.8(4)	C(18)-C(19)-N(26)	107.1(5)
C(5)-C(3)-C(6)	116.1(4)	C(20)-C(19)-N(26)	118.7(5)
C(3)-C(6)-C(7)	116.6(5)	C(19)-C(20)-C(21)	123.2(5)
C(3)-C(6)-C(8)	111.0(4)	C(19)-C(20)-C(25)	118.8(5)
C(3)-C(6)-O(9)	102.2(4)	C(21)-C(20)-C(25)	117.8(5)
C(7)-C(6)-C(8)	108.1(4)	C(20)-C(21)-C(22)	121.3(5)
C(7)-C(6)-O(9)	110.6(4)	C(21)-C(22)-C(23)	120.7(6)

C(8)-C(6)-O(9)	108.0(4)	C(22)-C(23)-C(24)	119.6(6)
B(1)-O(9)-C(6)	108.4(3)	C(23)-C(24)-C(25)	120.7(6)
B(1)-C(10)-C(11)	128.0(4)	C(20)-C(25)-C(24)	119.9(5)
B(1)-C(10)-C(18)	109.2(4)	B(1)-N(26)-C(19)	107.8(4)
C(11)-C(10)-C(18)	122.7(5)		

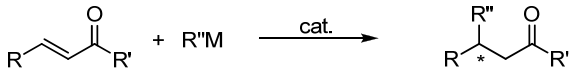
Chapter 2

Development of the Transition-Metal-Catalyzed Enantioselective Conjugate Allylation

I. Introduction

The conjugate addition of organometallic reagents to α,β-unsaturated carbonyl electrophiles is an important process for construction of carbon-carbon bonds in organic synthesis (Scheme 2.1).[1] Importantly, this process introduces a new stereocenter into the product, and therefore, development of asymmetric conjugate addition processes is an important area of research for the synthesis of non-racemic organic molecules. Not surprisingly then, many groups have been involved in this area of research, and many useful metal-catalyzed asymmetric conjugate addition processes have been developed.[1,2]

Scheme 2.1: General Metal-Catalyzed Conjugate Addition



Surprisingly, despite intense research in this area, the use of allyl nucleophiles in asymmetric conjugate addition is still an unsolved problem. Interestingly, while most

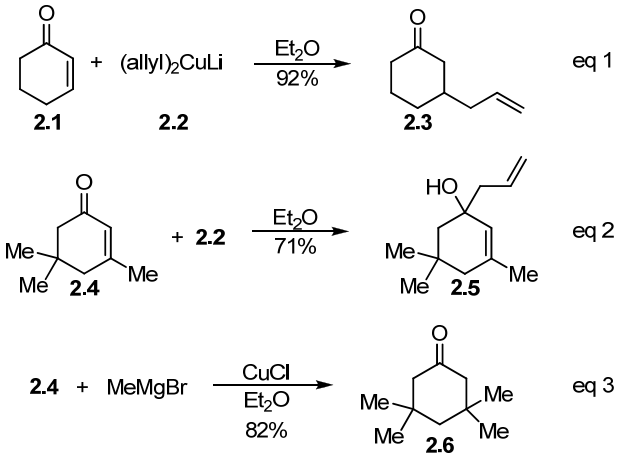
[1] (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 3, p 1105. (b) Kraus, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171.

[2] Reviews: (a) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (c) Sibi, M. K.; Shankar, M. *Tetrahedron* **2000**, *56*, 8033.

organocuprates[3] reliably afford conjugate addition over direct 1,2-addition, allylcuprates are a notable exception to this trend. The 1,4 to 1,2 selectivity for addition reactions with diallylcuprate is highly substrate dependent and often affords the 1,2-allylation product in preference to the conjugate addition product.[4] As depicted in Scheme 2.2, cyclohexenone (**2.1**) reacts readily with lithium diallylcuprate giving the conjugate addition product in good yield; however, isophorone (**2.4**) gave only the homoallylic alcohol product. In contrast, isophorone undergoes clean conjugate addition when using other Grignard reagents in the presence of a Cu-metal (Scheme 2.2, eq 3).[5] Clearly, Cu-based allyl nucleophiles are less reliable in conjugate addition reactions than their vinyl, aryl, and alkyl counterparts. Other methods have been developed to overcome this shortcoming with allyl nucleophiles; however, a general catalytic asymmetric conjugate allylation is elusive.

[3] Reviews: (a) Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393. (b) Nakamura, E.; Mori, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 3750.
[4] (a) House, H. O.; Fischer, Jr. W. F. *J. Org. Chem.* **1969**, *34*, 3615. (b) Majetich, G.; Casares, A.; Chapman, D.; Behnke, M. *J. Org. Chem.* **1986**, *51*, 1745.
[5] Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308.

Scheme 2.2: Reaction of Di(allyl)cuprate with Enones



II. Background

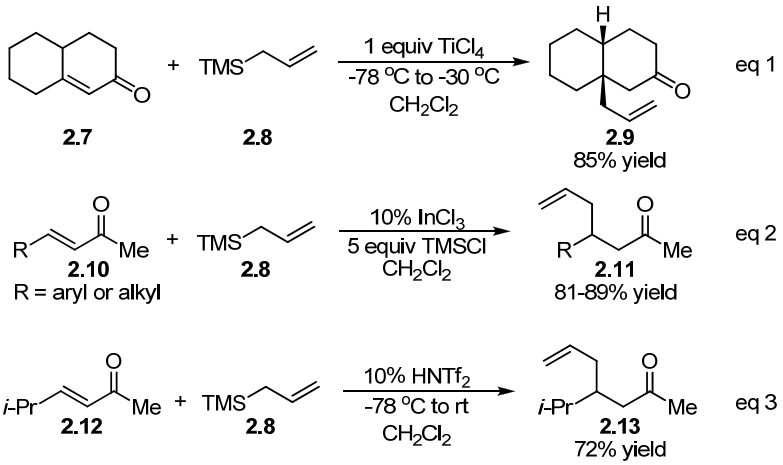
A. Non-Enantioselective Conjugate Allylation Processes

The earliest example of a reliable conjugate allylation was reported by Hosomi and Sakurai in 1978.[6] Using a stoichiometric amount of $TiCl_4$ as Lewis acid, allylic silanes undergo effective conjugate allylation with a variety of unsaturated ketones. One notable example is given in Scheme 2.3 (eq 1), where a sterically hindered angular allyl group can be installed in excellent yield. Catalytic variants of the Sakurai conjugate allylation have been developed using either $InCl_3$ or $HNTf_2$ as catalysts (Scheme 2.3, eq 2 and 3, respectively).[7,8] For the catalytic reaction with $InCl_3$, the addition of TMSCl is crucial. This phenomenon was suggested to result from trapping of an intermediate In-enolate by TMSCl to free the catalyst and drive equilibrium in this process. It should be

[6] Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1978**, *99*, 1673.
[7] (a) Lee, P. H.; Lee, K.; Sung, S. –Y.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8646. (b) Lee, P. H.; Seomoon, D.; Kim, S.; Nagaiah, K.; Damle, S. V.; Lee, K. *Synthesis* **2003**, 2189.
[8] Kuhnert, N.; Peverley, J.; Robertson, J. *Tetrahedron Lett.* **1998**, *39*, 3215.

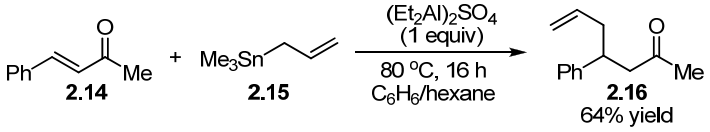
noted that $TiCl_4$ is not a competent catalyst under these conditions and must be used in stoichiometric amounts. Amberlyst 15 is also a suitable catalyst for intramolecular conjugate allylation when tethered allylic silanes are used.[9]

Scheme 2.3: Conjugate Allylation with Allylsilanes



In addition to allylsilane, allyltrimethylstannane is also an effective nucleophile in conjugate allylation when using 1 equiv of $(Et_2Al)_2SO_4$ as Lewis acid (Scheme 2.4).[10] However, this method does require somewhat more forcing conditions (80 °C reaction temperature) for successful reaction.

Scheme 2.4: Conjugate Allylation with Allyltrimethylstannane



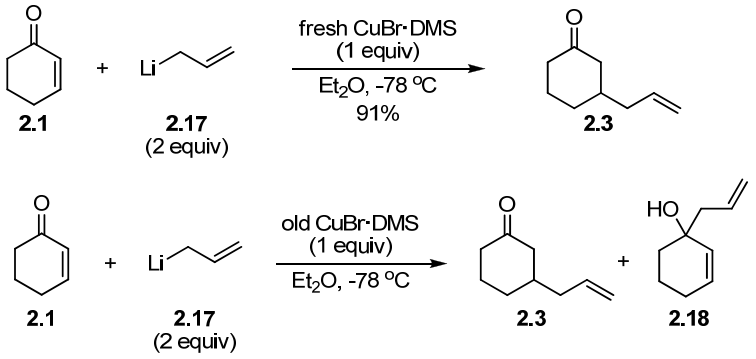
[9] Schinzer, D.; Ringe, K. *Synlett* **1994**, 463.
[10] Hosomi, A.; Iguchi, H.; Endo, M.; Sakurai, H. *Chem. Lett.* **1979**, 977.

Further study into the conjugate allylation with allylcuprates has led to improvements in the 1,4-selectivity when using these reagents. Studies by House and coworkers showed that the purity of the Cu salt used to prepare the cuprate affects the regioselectivity in the conjugate allylation.[11] When using freshly purified CuBr·DMS to form the allylcuprate, good yield of conjugate allylation product **2.3** was obtained (Scheme 2.5, eq 1); however, when older samples of CuBr·DMS were used, mixtures of 1,4- and 1,2-addition products were isolated. This was postulated to result from decomposition of the allylcuprate to allyllithium, facilitated by Cu(II) contaminants; allylithium preferentially gives 1,2-addition to the enone. Furthermore, even with freshly purified Cu-salts, the regioselectivity is highly dependent on the enone used in the reaction. However, a prediction of regioselectivity can be made based on the reduction potential (E_{red}) of the enone. If the enone has E_{red} that is -2.0 V or less negative, then conjugate allylation should be preferred over 1,2-addition. However, if the E_{red} is more negative than -2.0 V, the mode of addition cannot be predicted. It should be noted that E_{red} was initially used by House for predictive purposes because the mechanism for conjugate addition was believed to occur by a SET process at that time; this view of the reaction mechanism is no longer accepted.[3b,12] Hence, a correlation between E_{red} and reaction outcome is purely coincidental.

[11] House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443.

[12] For recent spectroscopic evidence for involvement of Cu(III) intermediates in cuprate chemistry, see: Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A.; Taylor, B. J. *J. Am. Chem. Soc.* **2007**, *129*, 7208. (b) Gärtner, T.; Henze, W.; Gschwind, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 11362.

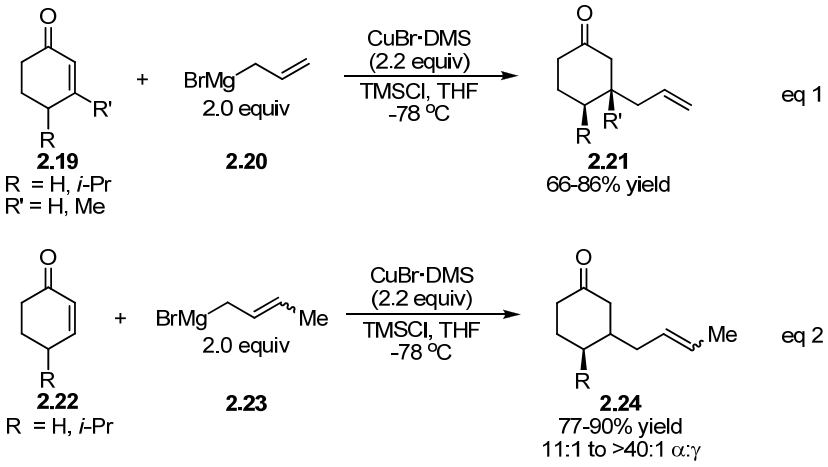
Scheme 2.5: Effect of Cu-Salt Purity in Conjugate Allylation



These problems associated with allylcuprates can be overcome by the use of allylic copper reagents with TMSCl as an additive (Scheme 2.6).[13] The use of (allyl)Cu·LiI or (allyl)Cu·$MgBr_2$, prepared using either allyllithium or allylmagnesium bromide, respectively, reliably affords the conjugate allylation product. TMSCl must be employed as an additive for successful reaction; in its absence, 1,2-addition is observed in low yield. TMSCl is known to accelerate Cu-mediated and Cu-catalyzed conjugate addition reactions.[3] Furthermore, when TMSCl is used in conjunction with higher or lower order allylcuprates, only 1,2-addition is observed. Crotyl and methallyl Grignard reagents also react with good regioselectivity with respect to the crotyl reagent. For cyclohexenone derivatives, crotylation α to the organometallic is observed (eq 2), while with cyclopentenone, crotylation γ to the organometallic results (not shown).

[13] (a) Lipshutz, B. H.; Ellsworth, E. L.; Dimcock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404. (b) Lipshutz, B. H.; Hackmann, C. *J. Org. Chem.* **1994**, *59*, 7437.

Scheme 2.6: Use of Allylic Copper Reagents in Conjugate Allylation



Other allylic organometallic reagents that have been employed for conjugate allylation include tantalum,[14] barium,[15] and indium.[16] Notably, in the cases of allyltantalum and allylbarium reagents, high selectivity for conjugate allylation over 1,2-addition is observed in the absence of additives. Furthermore, substituted allyltantalum reagents (i.e. crotyl or cinnamyl) give the branched products in good yield, whereas substituted allylic barium reagents afford the linear product.

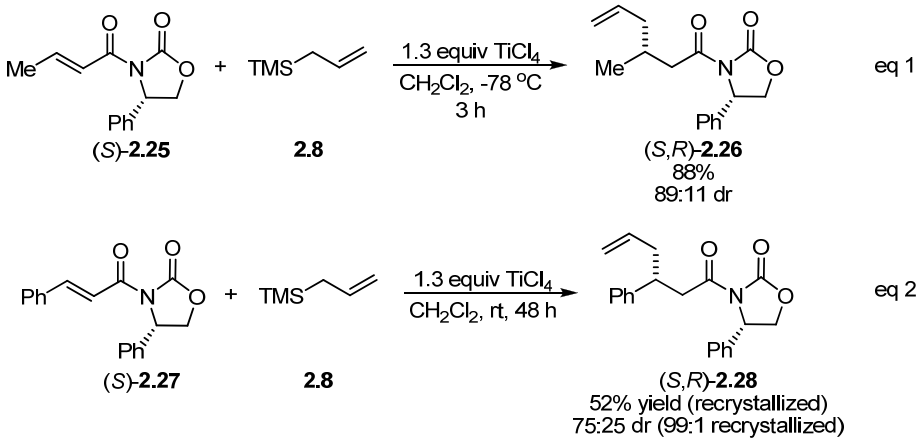
B. Asymmetric Conjugate Allylation Processes

Surprisingly, despite efforts to effect reliable conjugate addition of allylic nucleophiles, the addition of these nucleophiles with absolute stereochemical control is

[14] Shibata, I.; Kano, T.; Kanazawa, N.; Fukuoka, S.; Baba, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1389.
[15] Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, 6130.
[16] Lee, P. H.; Ahn, H.; Lee, K.; Sung, S. –Y.; Kim, S. *Tetrahedron Lett.* **2001**, *42*, 37.

currently limited to the use of chiral auxiliaries. Wu and co-workers[17] have shown that unsaturated chiral electrophiles **2.25** and **2.27**, bearing the Evans' chiral oxazolidinone auxiliary,[18] participate in the Sakurai conjugate allylation with good diastereocontrol (Scheme 2.7). The cinnamyl derived substrate **2.27** is allylated with lower diastereocontrol; however, recrystallization affords the pure diastereomer **2.28** in moderate yield. Furthermore, the auxiliary can be removed using LiOH to afford the carboxylic acid derivative.

Scheme 2.7: Asymmetric Sakurai Conjugate Allylation

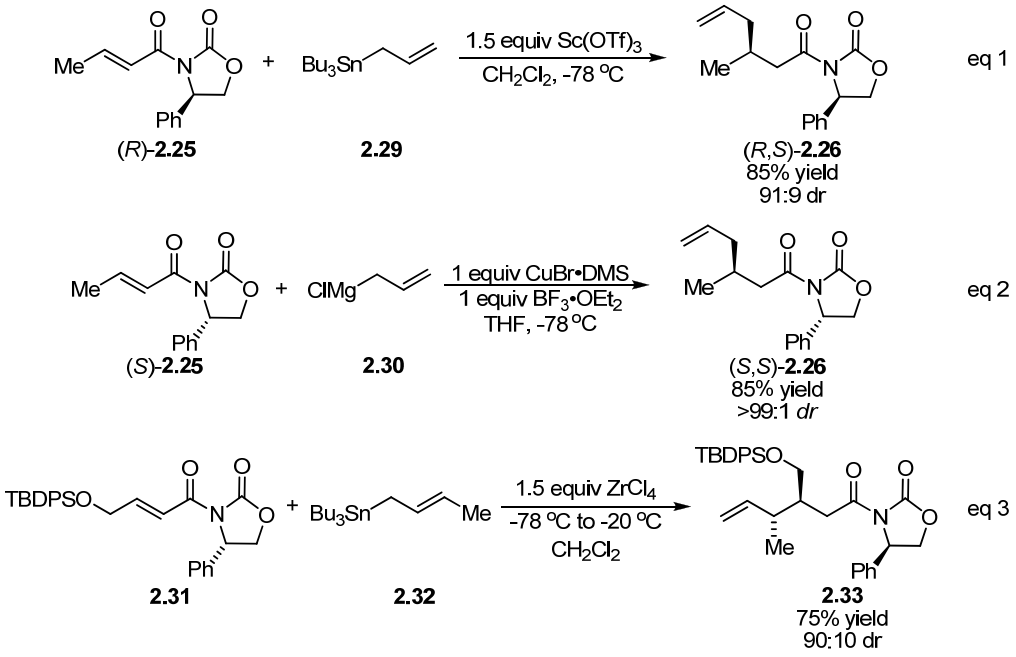


The Williams' group has also employed this auxiliary in asymmetric conjugate allylation using both allylic tributylstannane[19] and allyl Grignard[20] nucleophiles (Scheme 2.8). Notably, the choice of allylic nucleophile dictates which diastereomer is formed in

[17] Wu, M. –J.; Wu, C. –C.; Lee, P. –C. *Tetrahedron Lett.* **1992**, *33*, 2547.
[18] Reviews: (a) Evans, D. A.; Kim, A. S. In *Handbook of Reagents in Organic Synthesis: Reagents, Auxiliaries, and Catalysts for C-C Bonds;* Coates, R. M.; Denmark, S. E., Eds.; John Wiley & Sons: New York, 1999; pp 91-101. (b)Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3.
[19] Williams, D. R.; Mullins, R. J.; Miller, N. A. *Chem. Commun.* **2003**, 2220.
[20] Williams, D. R.; Kissel, W. S.; Li, J. J. *Tetrahedron Lett.* **1998**, *39*, 8593.

the reaction (eq 1 vs eq 2) thereby allowing access to either diastereomer from the same starting material. Note that these reactions require stoichiometric amounts of Lewis acid, and in the case of Grignard reagents, 1 equiv of CuBr·DMS is required. This is not surprising on the basis of the findings of Lipshutz and co-workers[13] who determined that only allylic copper reagents reliably afford conjugate allylation products (see page 106). Finally, crotylstannanes can also be employed when Zr is used as the Lewis acid (Scheme 2.8, eq 3). Only an *anti*-relationship between the β and γ stereocenters is observed in this case.

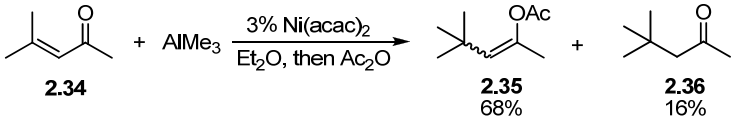
Scheme 2.8: Asymmetric Conjugate Allylation with Allylic Stannanes and Allylmagnesium Chloride



C. Conjugate Addition Reactions Catalyzed by Group 10 Transition Metals

Seminal work by Mole and co-workers[21] established the utility of Ni as a catalyst for conjugate addition of $AlMe_3$ to enones (Scheme 2.9). In the presence of $Ni(acac)_2$, $AlMe_3$ adds to enone **2.34**, in the 1,4-sense, giving vinyl acetate **2.35** after addition of Ac_2O. Notably, in the absence of the Ni(II) salt, only 1,2-addition of $AlMe_3$ to **2.34** is observed. Since this initial report, Ni-catalysis has been applied to the conjugate addition of organozirconium,[22] organozinc,[23] organoboron,[24] organostannane,[25] and organoindium[26] reagents. Despite the use of Ni(II) salts as catalysts, the active catalyst is believed to be Ni(0), which is generated *in situ* from the reduction of Ni(II) under the reaction conditions.[22]

Scheme 2.9: Ni-Catalyzed Conjugate Addition of $AlMe_3$ to Enones



2.34 **2.35** 68% **2.36** 16%

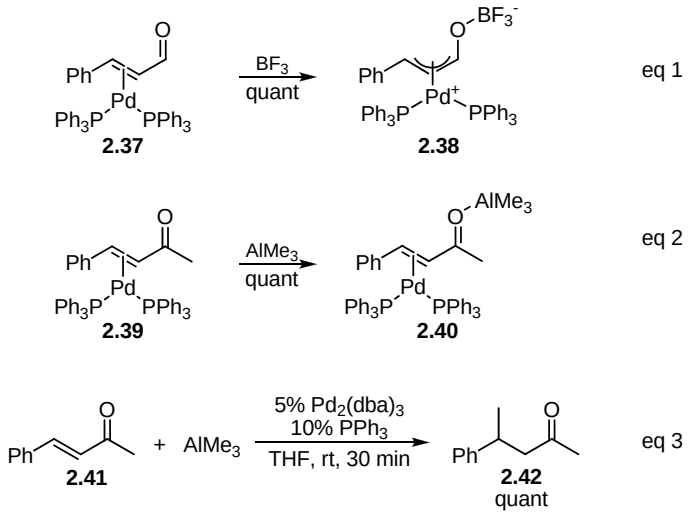
This class of conjugate addition reactions requires a Lewis acid for successful reaction. The role of the Lewis acid in this process has been examined by Kurosawa and

---

[21] Jefferey, E. A.; Meisters, A.; Mole, T. *J. Organomet. Chem.* **1974**, *174*, 365.
[22] Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333.
[23] (a) Greene, A. E.; Lansard, J. –P.; Luche, J. –L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931. (b) Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516. (c) For a Pd(0)-catalyzed variant see: Marshall, J. A.; Herold, M.; Eidam, H. S.; Eidam, P. *Org. Lett.* **2006**, *8*, 5505.
[24] (a) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1541. (b) Shirakawa, E.; Yasuhara, Y.; Hayashi, T. *Chem. Lett.* **2006**, *35*, 768.
[25] Grisso, B. A.; Johnson, J. R.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160.
[26] Pérez, I.; Sestelo, J. P.; Maestro, M. A.; Mouriño, A.; Sarandeses, L. A. *J. Org. Chem.* **1998**, *63*, 10074.

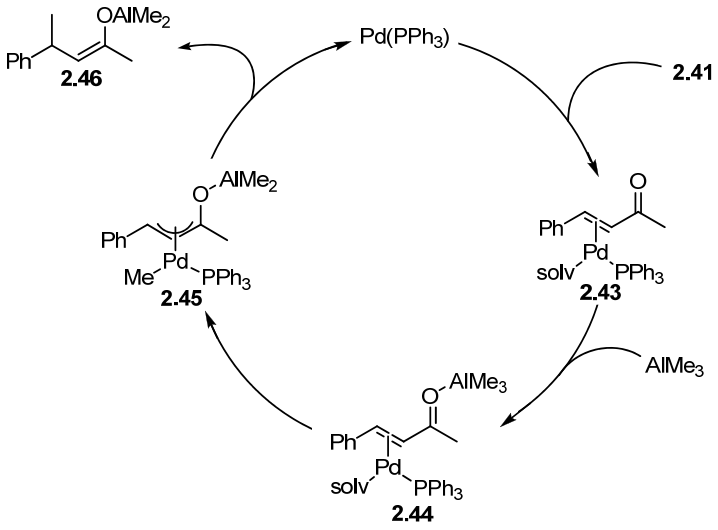
co-workers.[27] When enal or enone Pd-complexes **2.37** or **2.39** are treated with various Lewis acids, complexes **2.38** or **2.40** are isolated in near quantitative yields, respectively (Scheme 2.10, eq 1 and 2). Furthermore, in the presence of 5 mol% $Pd_2(dba)_3$ and 10 mol% PPh_3, effective conjugate addition of $AlMe_3$ to enone **2.41** is observed (eq 3). Based on these observations, a plausible catalytic cycle for this transformation was developed by the authors, which correlates to the findings of Mackenzie[25] (Scheme 2.11). Activation of $(PPh_3)Pd$(enone) complex (**2.43**) by a Lewis acid ($AlMe_3$) enables oxidative addition of the metal to the bound enone affording **2.44**. Subsequent transmetalation and reductive elimination generates the aluminum enolate **2.46**, which is quenched upon workup to afford the observed product (**2.42**).

Scheme 2.10: Reaction of L_2Pd(enone) Complexes with Lewis Acids



[27] (a) Ogoshi, S.; Yoshida, T.; Nishida, T.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 1944. (b) Morita, M.; Inoue, K.; Ogoshi, S.; Kurosawa, H. *Organometallics* **2003**, *22*, 5468. (c) Ogoshi, S.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2003**, *125*, 9020.

Scheme 2.11: Mechanism of the Pd-Catalyzed Conjugate Addition of $AlMe_3$



This mechanism for conjugate addition catalyzed by group 10 metals, which relies on redox chemistry at the metal center, is in stark contrast to the extensively studied conjugate addition of organoboron, organosilicon, organotin, and organotitanium reagents catalyzed by Rh(I) complexes.[28] More recently Pd(II) complexes have also been shown to effect conjugate addition when using boronic acids[29] or organosiloxanes[30] as nucleophiles. In these systems, Rh(I)/Rh(III) or Pd(0)/Pd(II) catalytic cycles are not believed to be responsible for product formation. Rather, transmetalation of the nucleophile to the Rh(I) or Pd(II) salt occurs, followed by addition to the α,β-unsaturated

[28] Review: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.
[29] (a) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem. Int. Ed.* **2003**, *42*, 2768. (b) Lu, X.; Lin, S. *J. Org. Chem.* **2005**, *70*, 9651. (c) Nishikita, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317. (d) Gini, F.; Hessen, B.; Minaard, A. J. *Org. Lett.* **2005**, *7*, 5309. (e) Horiguchi, H.; Tsurugi, H.; Satoh, T.; Miura, M. *J. Org. Chem.* **2008**, *73*, 1590. (f) He, P.; Lu, Y.; Dong, C. –G.; Hu, Q. –S. *Org. Lett.* **2007**, *9*, 343. (g) Yammamoto, T.; Iizuka, M.; Ohta, T.; Ito, Y. *Chem. Lett.* **2006**, *35*, 198 and references therein.
[30] (a) Lerebours, R.; Wolf, C. *Org. Lett.* **2007**, *9*, 2737. (b) Gini, F.; Hessen, B.; Feringa, B. L.; Minaard, A. J. *Chem. Commun.* **2007**, 710. (c) Denmark, S. E.; Amishiro, N. *J. Org. Chem.* **2003**, *68*, 6997.

carbonyl electrophile giving a Rh(I) or Pd(II) enolate. Quench of the enolate by a proton source, usually water, releases the product and a Rh(I) or Pd(II) salt.

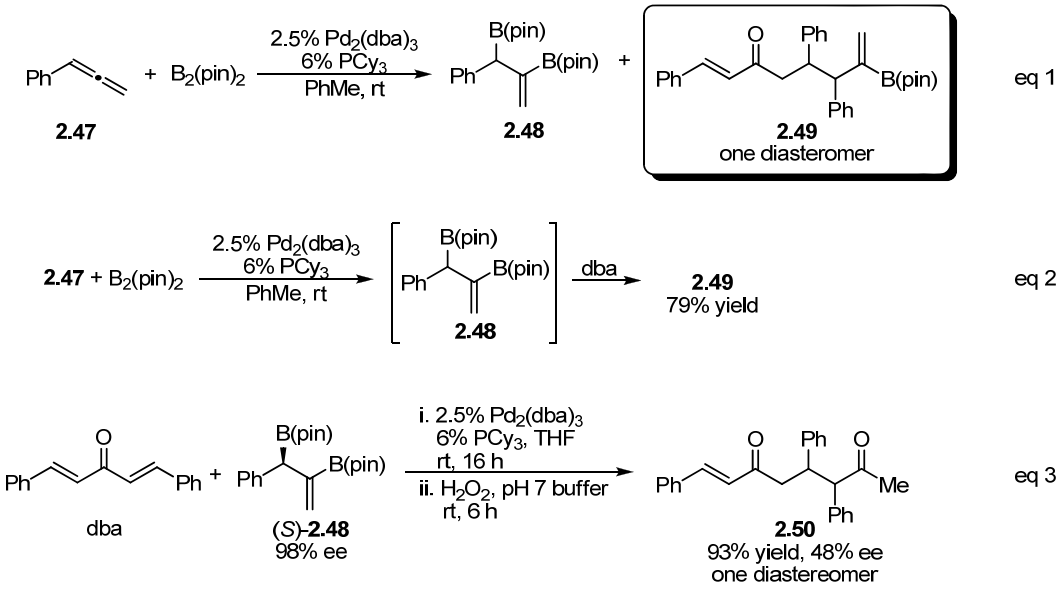
III. Discovery and Development of a Transition-Metal-Catalyzed Conjugate Allylation with Allylboronate Ester Nucleophiles[31]

A. Reaction Discovery

While developing the asymmetric allene diboration described in Chapter 1, a side-product was isolated from the reaction and was determined to be **2.49** (Scheme 2.12, eq 1). This product may arise from conjugate addition of allylboronate ester **2.48** to dibenzylidene acetone (dba), which was present in solution from the precatalyst. Furthermore, if dba was added to the diboration reaction after completion, **2.48** was not observed in the ^{1}H NMR spectrum of the unpurified reaction mixture, and **2.49** was isolated in good yield (Scheme 2.12, eq 2). Control experiments verified that both $Pd_2(dba)_3$ and PCy_3 were required for conversion to **2.49**. Mixing **2.47** with dba in toluene without both of these reagents resulted in no conversion. Additionally, the Pd-catalyzed reaction of enantiomerically pure **2.48** with dba, followed by oxidation of the vinylboronate functionality, afforded **2.50** as a single diastereomer in good yield (eq 3). However, the chirality transfer in this process was low.

[31] (a) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214. (b) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978.

Scheme 2.12: Conjugate Allylation with Allene Diboration Products



To study this reaction further, dba was treated with commercially available allylboronic acid pinacol ester (**2.51**) using $Pd_2(dba)_3/PCy_3$ as catalyst (Scheme 2.13). This reaction resulted in the formation of conjugate allylation product **2.52** in 79% yield after only 1 h at room temperature. Again, both Pd and phosphine were required for conjugate allylation. Interestingly, only dba was reactive under these conditions. When applying this catalyst system to conjugate allylation of the α,β-unsaturated electrophiles depicted in Figure 2.1, no conjugate allylation was detected. In addition, heating these reactions to 65 ^{o}C in THF did not improve reactivity.

Scheme 2.13: Pd-Catalyzed Conjugate Allylation of Dba

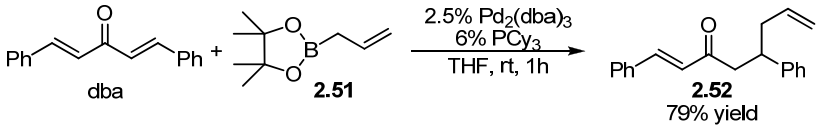
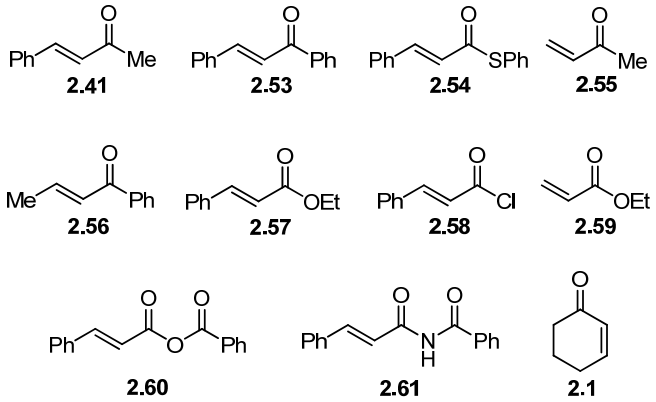


Figure 2.1: Electrophiles Tested in the Pd-Catalyzed Conjugate Allylation

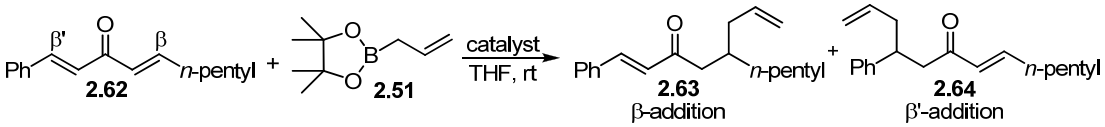


B. Reaction Development

Discovery of a conjugate allylation process that proceeded in the presence of a transition metal catalyst and a phosphine ligand provided an opportunity to develop an asymmetric catalytic conjugate allylation, whereby a chiral ligand could be used to control facial selectivity in the reaction. However, because only dialkylidene ketones, such as dba, were reactive electrophiles, unsymmetrical dialkylidene ketone **2.62** was prepared and subjected to the conjugate allylation procedure (Table 2.1). For conjugate allylation of **2.62** to be synthetically useful, the catalyst for the reaction must effect chemoselective addition of the allyl nucleophile to either the β- or β′-position of the dialkylidene ketone selectively. To achieve this goal, a survey of group 10 metals, in

conjunction with phosphine ligands, were analyzed in the conjugate allylation of **2.62**. The results of this investigation are given in Table 2.1.

Table 2.1: Catalyst Optimization for the Conjugate Allylation of 2.62



entry	metal	ligand	time (h)	β:β′ [a]	% yield[b]
1	2.5% $Pd_2(dba)_3$	6% PCy_3	2	n/a	< 5
2	2.5% $Pd_2(dba)_3$	6% PCy_3	16	73:27	67
3	2.5% $Pd_2(dba)_3$	6% $P(NMe_2)_3$	2	50:50	76
4	2.5% $Pd_2(dba)_3$	6% PPh_3	2	50:50	18
5	2.5% $Pd_2(dba)_3$	6% $P(OPh)_3$	2	36:64	17
6	10% $Ni(cod)_2$	20% PCy_3	4	88:12	82
7	10% $Ni(cod)_2$	20% $P(NMe_2)_3$	4	71:29	81
8	10% $Ni(cod)_2$	20% PPh_3	4	70:30	49
9	10% $Ni(cod)_2$	20% $P(OPh)_3$	4	52:48	55

[a]Chemoselectivity determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b]Yield of conjugate allylation product after silica gel chromatography. Isolated as a mixture of constitutional isomers. Value is an average of at least 2 experiments.

Under Pd-catalysis, when a bulky, Lewis basic ligand was employed, the allylation was sluggish, but allylation preferentially occurred at the alkylidene site (β-position) of the substrate, giving **2.63** in a modest 73:27 ratio (entry 2). HMPT proved to be an efficient ligand in terms of reaction rate; however, no chemoselection was observed in this case (entry 3). Notably, when using Ni as the catalyst, good yield of the

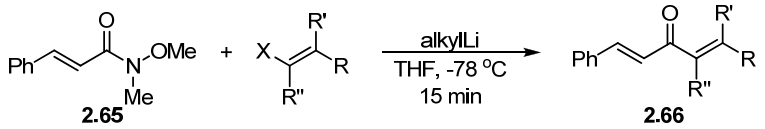
conjugate allylation product could be obtained in only 4 h at room temperature (entry 6). Furthermore, the highest chemoselectivity was obtained in this case, favoring conjugate allylation to the alkylidene site of **2.62** in an 88:12 ratio. Under Ni-catalysis, a drop in both chemoselectivity and rate was observed when using phosphines of decreased Lewis basicity (entries 6-9).

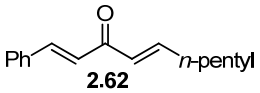
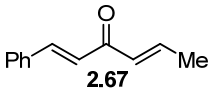
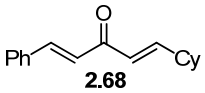
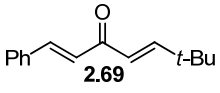
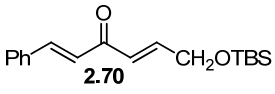
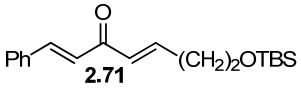
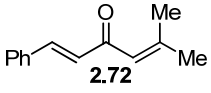
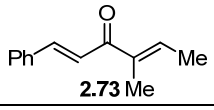
C. Scope and Utility of the Ni-Catalyzed Conjugate Allylation

With identification of a Ni-catalyst that afforded chemoselective conjugate allylation to the alkylidene unit of unsymmetrical dialkylidene ketone **2.62**, analysis of the scope of this catalyst commenced. A class of unsymmetrical dialkylidene ketones was synthesized where each ketone contained a benzylidene group, for substrate activation, and a variable alkylidene group (**2.66**, Table 2.2). These ketones were most conveniently prepared using the Weinreb[32] amide ketone synthesis. Those used in the conjugate allylation reaction are shown in Table 2.2. In general, the ketones were prepared in good yields, where yields were optimal when vinyl iodides were used as precursors to the vinyl lithium nucleophile. Furthermore, *n*-BuLi could be used for the Li/halogen exchange when using vinyl iodides (entries 1 and 3-6), while *t*-BuLi was required for the Li/halogen exchange when employing vinyl bromides (entries 2, 7, and 8); use of *n*-BuLi in the Li/halogen exchange step with vinyl bromides led to inferior yields. In addition, Grignard reagents were ineffective in the ketone synthesis.

[32] Nahm, S.; Weinreb, S., M. *Tetrahedron Lett.* **1981**, *22*, 3815.

Table 2.2: Synthesis of Unsymmetrical Dialkylidene Ketones



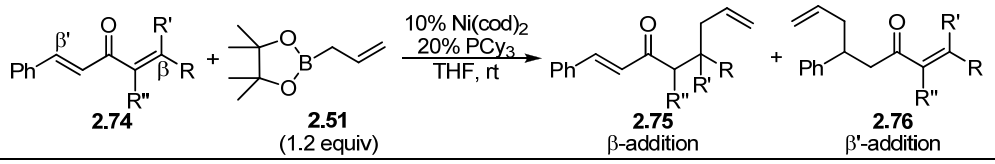
entry	X	alkylLi	product	% yield
1	I	*n*-BuLi	 **2.62**	91
2	Br	*t*-BuLi	 **2.67**	76
3	I	*n*-BuLi	 **2.68**	96
4	I	*n*-BuLi	 **2.69**	86
5	I	*n*-BuLi	 **2.70**	75
6	I	*n*-BuLi	 **2.71**	87
7	Br	*t*-BuLi	 **2.72**	53
8	Br	*t*-BuLi	 **2.73**	53

With access to a variety of unsymmetrical dialkylidene ketones, the substrates prepared in Table 2.2 were subjected to the conjugate allylation reaction using $Ni(cod)_2/PCy_3$ as catalyst. The results of this survey are shown in Table 2.3. When methyl-substituted ketone **2.67** or *t*-butyl-substituted ketone **2.69** was used in the conjugate allylation, high chemoselectivity was observed in the allylation (entries 2 and

4). Furthermore, when trisubstituted alkylidene substrates **2.72** and **2.73** were used, complete chemoselectivity was observed; however, the reaction temperature had to be increased to 65 ^{o}C to achieve useful conversions (entries 8 and 9). The result in entry 8 is notable since the reaction installs the allyl group at the more sterically encumbered carbon, allowing access to an all-carbon quaternary center. Alkoxy groups were also tolerated in the reaction (entries 5 and 6). Notably, in the presence of an allylic TBS-ether, conjugate allylation proceeded in good yield (entry 6) even though allylic ethers are known to participate in allylic substitution reactions with boronic acids under Ni-catalysis.[33] However, chemoselectivity was low for this substrate.

[33] Chung, K. G.; Miyake, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 15.

Table 2.3: Substrate Scope in the Ni-Catalyzed Conjugate Allylation



entry	R	R′	R″	time (h)	β:β′ [a]	% yield[b]
1	*n*-pentyl	H	H	4	88:12	82
2	Me	H	H	24	95:5	75
3	Cy	H	H	4	83:17	83
4	*t*-Bu	H	H	4	>95:5	74
5	CH_2OTBS	H	H	24	61:39	66
6	CH_2CH_2OTBS	H	H	7	85:15	82
7	Ph	H	H	4	n/a	74
8[c,d]	Me	Me	H	24	>95:5	80
9[c]	Me	H	Me	24	>95:5	76[e]

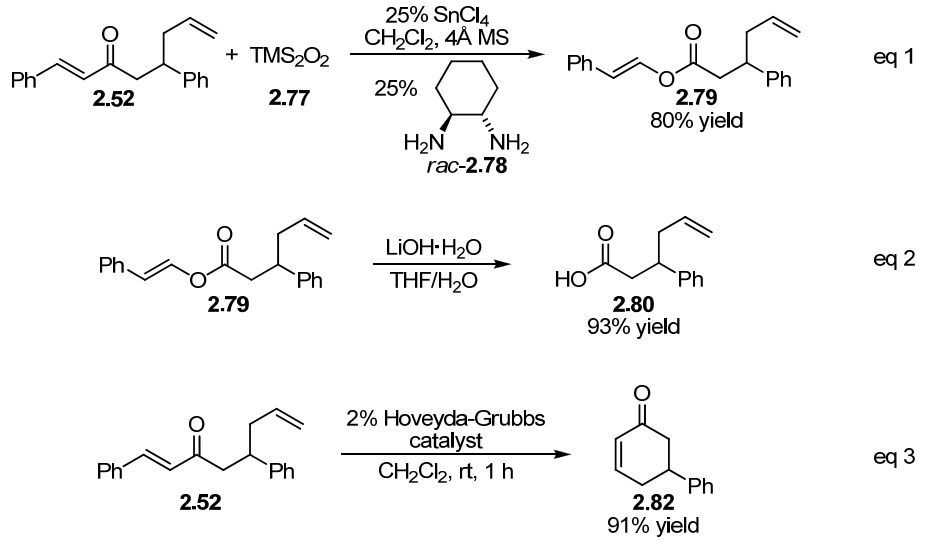
[a]Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b]Isolated yield after silica gel chromatography. Yield represents an isomeric mixture and is an average of at least two experiments in each case. [c]Reaction was performed at 65 °C. [d]2.0 equiv of **2.51** was used. [e]Product consists of a 1.4:1 diastereomeric mixture.

To further develop the utility of this conjugate allylation protocol, a method for removal of the activating benzylidene unit was sought. A Sn-catalyzed Baeyer-Villiger reaction, developed by Shibasaki[34] and co-workers, furnished unsaturated ester **2.79** with complete chemo- and regioselectivity (Scheme 2.14, eq 1). Furthermore, the ester could be saponified with LiOH in excellent yield (Scheme 2.14, eq 2). In addition to cleavage of the benzylidene activating group, ring-closing metathesis was used to access 5-

[34] Göttlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971.

substituted cyclohexenone **2.81** (Scheme 2.14, eq 3). The Hoveyda-Grubbs[35] second generation catalyst was the optimal metathesis catalyst in this case.

Scheme 2.14: Transformations of the Benzylidene Activating Group



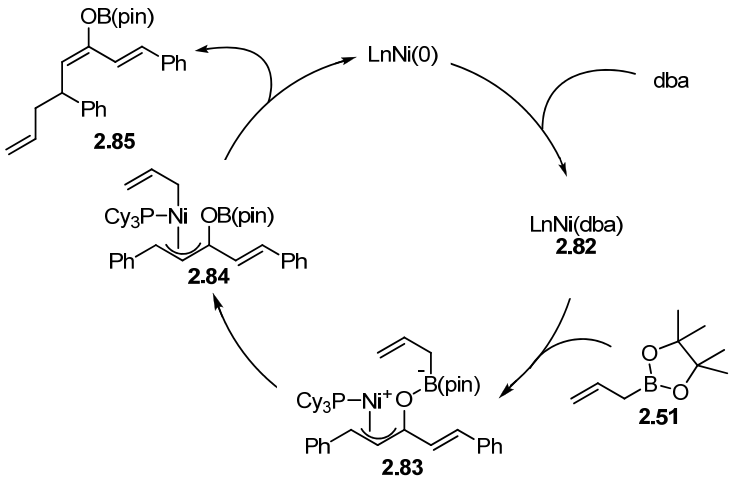
D. Mechanistic Aspects of the Ni-Catalyzed Conjugate Allylation

A reasonable catalytic cycle for the conjugate allylation is shown in Scheme 2.15. Based off of the work of Kurosawa[27] and Mackenzie[25] on the Pd- and Ni-catalyzed conjugate addition reaction of enones (see section II.C, page 110), allylboronate ester **2.51** likely acts as a Lewis acid to facilitate oxidative addition of Ni(0) to dba, furnishing LNi(allyl) complex **2.83**. Subsequent transmetalation would afford bis(allyl)Ni-complex **2.84** Reductive elimination from **2.84** gives the product masked as a boron enolate (**2.85**), which is quenched upon workup. In support of this hypothesis, when $Pd(TFA)_2$ or

[35] Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

$Ni(acac)_2$ was used in the conjugate allylation, no products were observed, indicating that M(0) is likely the active catalyst in the reaction. When Ni(0) was generated *in situ* by treatment of $Ni(acac)_2$ with DIBAL,[36] before addition of **2.51** and **2.62**, conjugate allylation was observed, further implicating M(0) as the active catalyst.

Scheme 2.15: Proposed Catalytic Cycle for the Conjugate Allylation

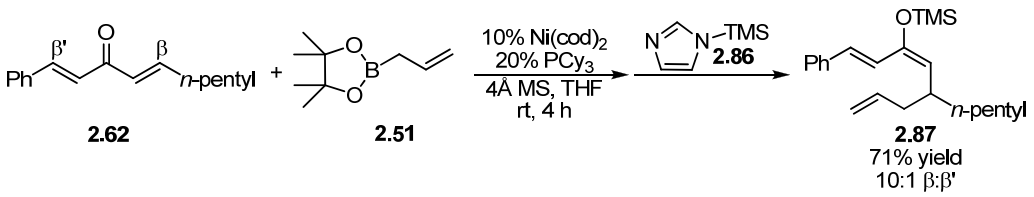


Attempts to trap the boron enolate intermediate, after the conjugate allylation was complete, were successful and informative (Scheme 2.16). In this experiment, conjugate allylation was performed in the presence of 4Å MS and subsequently quenched by the addition of *N*-(trimethylsilyl)imidazole (**2.86**).[37] Silyl enol ether **2.87** was isolated from the reaction mixture as a single olefin isomer. NOESY analysis of **2.87** verified the *E*-

[36] DIBAL is known to reduce Ni(II) to Ni(0). See: Krysan, D. J.; Mackenzie, P. B. *J. Org. Chem.* **1990**, *55*, 4229 and references therein.
[37] For the use of *N*-(trimethylsilyl)imidazole for silylation of boron enolates, see: Hooz, J.; Oudenes, J. *Tetrahedron Lett.* **1983**, *24*, 5695.

configuration of the silyl enol ether. When TMSCl was used in the trapping step, **2.87** was not observed, and only the ketone product was isolated.

Scheme 2.16: Trap of the Intermediate Boron Enolate

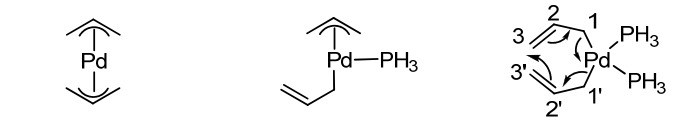


The enhanced reactivity of dialkylidene ketones relative to simple enones must be the result of a reduced energy barrier for one of the elementary steps in the catalytic cycle by the additional alkene unit of the DAK. While the oxidative addition or transmetalation steps may be facilitated by the additional alkene present in the substrate, we propose that acceleration of the reductive elimination step is responsible for the enhanced reactivity of dialkylidene ketones. This proposal is on the basis of the calculated reductive elimination barriers for bis(allyl)Pd-complexes (Figure 2.2).[38] Of the three possibilities, it is calculated that in the presence of donor ligands, reductive elimination from bis(η^1-allyl)Pd-complex **2.90** is the lowest energy pathway. While complex **2.90** is slightly higher in energy relative to **2.88** or **2.89**, **2.90** has the opportunity to undergo a [3,3′]-reductive elimination pathway as depicted in Figure 2.2. Reductive elimination from **2.90** is calculated to occur via this process rather than through direct

[38] Mendez, M.; Cuerva, J. M.; Gomez-Bengoa, E.; Cardenas, D. J.; Echavarren, A. M. *Chem. –Eur. J.* **2002**, *8*, 3620.

coupling of carbons 3 and 3′. Thus reductive elimination is significantly more facile from **2.90** relative to **2.88** or **2.89**.

Figure 2.2: Calculated Reductive Elimination Barriers for Bis(allyl)Pd-Complexes[38]



2.88 Ea = 36.6 kcal/mol

2.89 Ea = 23.4 kcal/mol

2.90 Ea = 8.5 kcal/mol

Based on this data, an analogous mode of reductive elimination can be envisioned in the conjugate allylation from intermediate **2.91** (Scheme 2.17, eq 1). Within the proposed catalytic cycle, **2.91** is formed after oxidative addition and transmetalation. As depicted in Scheme 2.17, **2.91** may undergo reductive elimination through a [3,3′]-reductive elimination pathway without formation of a higher energy bis(η^1-allyl)Ni(PR_3)$_2$ complex. This process is not available to enones lacking the extra alkene present in dialkylidene ketones, which may explain their resistance to reaction in the conjugate allylation. To ascertain if this scenario was feasible, Dr. Shubin Liu[39] performed DFT calculations on model system **2.92** using the B3LYP[40] method (Scheme 2.17, eqs 2 and 3).[31] The Stuttgard RSC 1997 ECP basis set[41] was used for Pd, and 6-311+G*[42] was used for other elements. These calculations verified that reductive elimination through a

[39] Division of Research Computing, Information Technology Services, University of North Carolina, Chapel Hill, NC 27599

[40] (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

[41] Bergner, A.; Dolg, M.; Kuechle, W.; Stoll, H.; Preuss, H. *Mol. Phys.* **1993**, *80*, 1431.

[42] Krishnan, R.; Brinkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.

[3,3′]-pathway (eq 2) has a remarkably low barrier (1.52 kcal/mol). Replacement of the pendant alkene with a methyl group increased the barrier significantly (Scheme 2.17, eq 3). In addition, the calculations predicted that 1,2-addition (**2.94**) and not 1,4-addition (**2.95**) should predominate in the unactivated enone. Figure 2.3 shows the calculated transition state for the reductive elimination of **2.92**. This proposal predicts that the *E*-configured boron enolate should be produced in the reaction, which correlates nicely to the observed *E*-configuration of silyl enol ether **2.87**.

Scheme 2.17: Calculated Reductive Elimination Barriers in the Conjugate Allylation

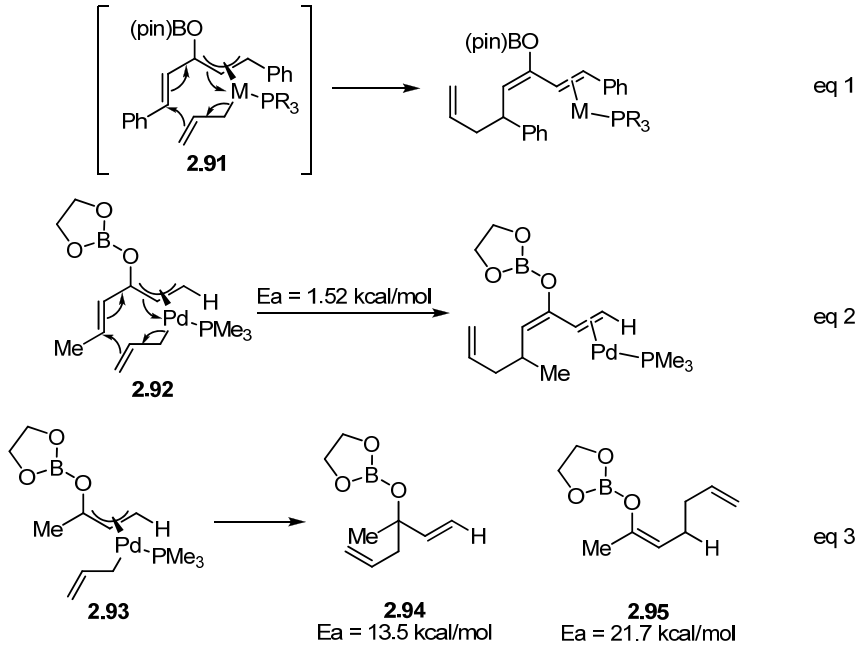
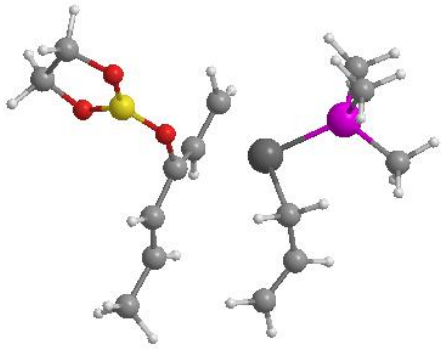


Figure 2.3: Calculated Transition Structure for the Reductive Elimination from 2.92

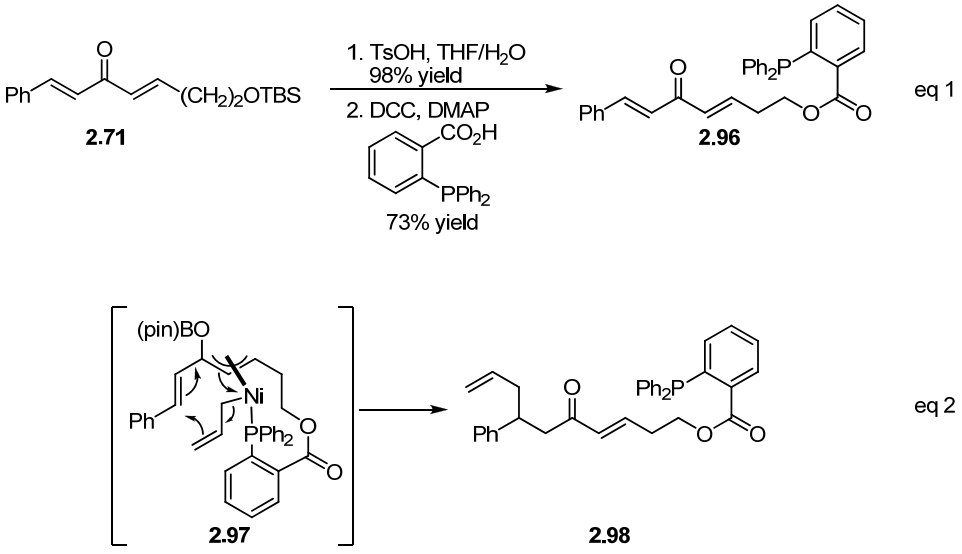


With calculated evidence for the facilitation of the reductive elimination step via a [3,3′]-reductive elimination pathway, experimental evidence to support these calculations was sought. Therefore, a dialkylidene ketone bearing an internal phosphino group (**2.96**) was prepared from **2.71** (Scheme 2.18, eq 1). It was postulated that if this internal phosphino group served as a ligand for Ni in the conjugate allylation, it should direct oxidative addition of the metal catalyst to the proximal alkene of **2.96**. If this was the case, and the [3,3′]-reductive elimination proceeded as proposed above, then conjugate allylation should occur at the distal alkene of **2.96**, giving **2.97**, and ultimately furnish **2.98** (Scheme 2.18, eq 2). Subjection of ketone **2.96** to the conjugate allylation reaction, in the absence of any external phosphine ligand, gave conjugate allylation exclusively at the benzylidene site in **2.96** (Scheme 2.19, eq 1).[43] No evidence for conjugate allylation

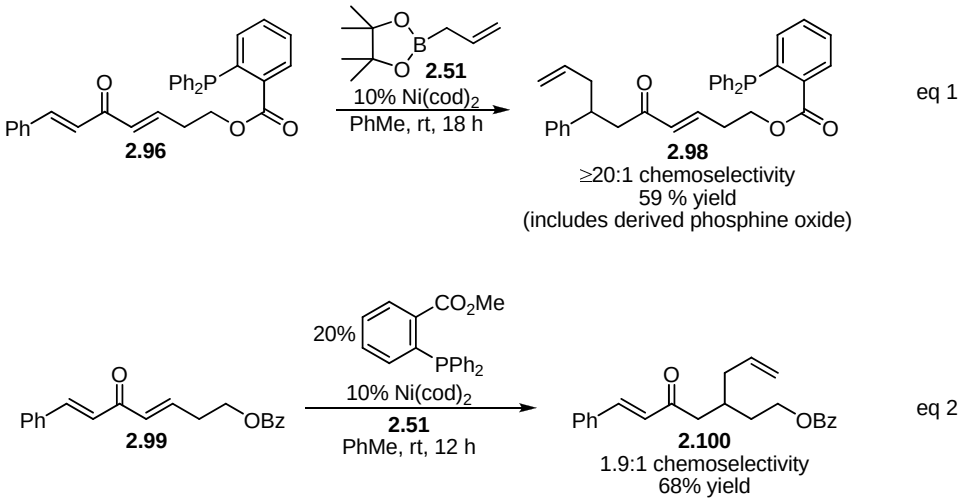
[43] Note that in addition to the conjgate allylation product **2.98** some of the derived phosphine oxide was isolated due to oxidation of **2.98** during purification.

to the alkene proximal to the phosphine directing group was observed. Furthermore, a control experiment using dialkylidene ketone **2.100** as the substrate proceeded with little chemoselection, verifying that the phosphino group in **2.96** was responsible for the high chemoselectivity (Scheme 2.19, eq 2).

Scheme 2.18: Analysis of a Phosphino-Directing Dialkylidene Ketone



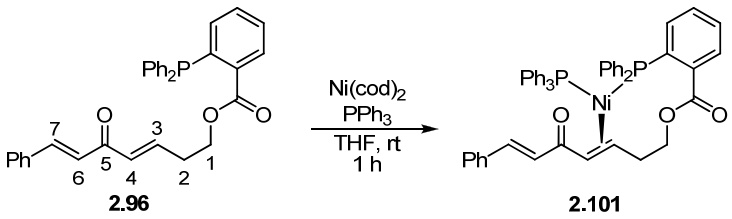
Scheme 2.19: Conjugate Allylation of a Phosphine Containing DAK



The experiments outlined in Scheme 2.19 offer further support for the proposed [3,3′]-reductive elimination pathway. However, the possibility that the tether in **2.96** may be long enough to direct the Ni-catalyst to the distal alkene in the substrate could not be ruled out. If this is the case, **2.98** may be formed by oxidative addition to the distal olefin in **2.96** followed by transmetalation and direct reductive elimination. To ascertain which olefin of **2.96** may coordinate to Ni, complex **2.101** was prepared (Scheme 2.20). When mixing equimolar amounts of **2.96**, $Ni(cod)_2$, and PPh_3 in THF at room temperature, complex **2.101** was formed. While suitable crystals for X-ray diffraction could not be obtained, NMR analysis of the red solid, when dissolved in solution, allowed for verification of the structure of **2.101**. Proton and carbon assignments were made by ^{1}H, ^{13}C, COSY, HSQC, and NOESY spectroscopic analyses. The hydrogen atoms at C3 and C4 in **2.101** exhibited an upfield shift of $\Delta\delta$ 3.01 ppm and $\Delta\delta$ 2.45 ppm, respectively relative to **2.96**. Likewise the carbon resonances for C3 and C4 moved to higher field by

Δδ 71.6 ppm and Δδ 60.2 ppm relative to starting material. In contrast, the hydrogen atoms at C6 and C7 of **2.101** exhibited a less substantial perturbation (Δδ 1.01 ppm and Δδ <0.05 ppm). Similarly, the carbon resonances for C6 and C7 were relatively unaffected, showing Δδ 0.6 ppm and Δδ 1.8 ppm, respectively. In addition to affecting the alkene hydrogens, the metal association also affected the chemical shift of the hydrogen atoms at C2 and C1. The proton resonance at C2 of **2.101** experienced a substantial upfield shift (Δδ 0.76 ppm), and the protons at C1 in the metal complex were now diastereotopic, one moving 0.72 ppm downfield and the other 0.44 ppm upfield. Collectively, these spectroscopic changes observed when **2.96** was treated with $Ni(cod)_2$ and PPh_3, were consistent with Ni binding to the alkene adjacent to the directing group. Other spectroscopic features were also consistent with this formulation; the ^{31}P NMR showed two doublet resonances at 41.21 ppm and 28.59 ppm (J = 32 Hz).

Scheme 2.20: Synthesis of (PPh_3)Ni(2.96) Complex



The identity of complex **2.101** and the chemoselectivity in the conjugate allylation of **2.96** provides further support for the validity of a [3,3′]-reductive elimination pathway

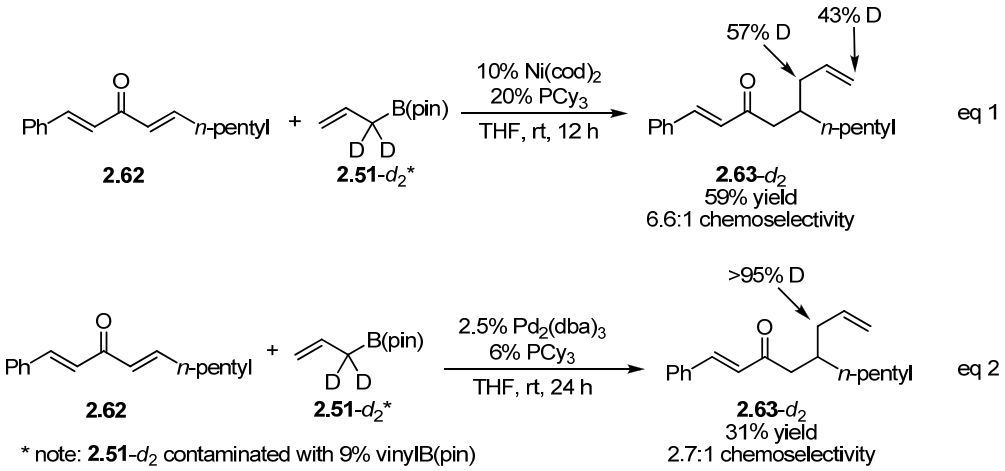
operating in the conjugate allylation of dialkylidene ketones. This then may explain the enhanced reactivity of DAKs relative to other enones.

To further investigate the intermediate bis(allyl)Ni-complexes formed in the conjugate allylation, the reaction was carried out using deuterium labeled allylboronic acid pinacol ester (**2.51**-d_2, Scheme 2.21). Interestingly, under Ni-catalysis (eq 1), scrambling of the deuterium label was observed in the product; however, under Pd-catalysis (eq 2), the site of the deuterium label was retained in the product. Since there is good evidence that transmetalation of allyl groups occurs via an S_E'-type mechanism,[44] transmetalation from complex **2.102** should afford **2.103** with the label at the vinylic position (Scheme 2.22). When M=Pd, [3,3′]-reductive elimination from **2.103** would furnish the retained label in the product. However, when M = Ni, η^1-η^3-η^1 allyl isomerization, presumably through **2.104**, likely occurs faster than reductive elimination and leads to scrambling of the label. The lower yields obtained in the reactions using **2.51**-d_2 were attributed to the presence of vinylboronic acid pinacol ester, which was a contaminant in **2.51**-d_2 resulting from its preparation.[45]

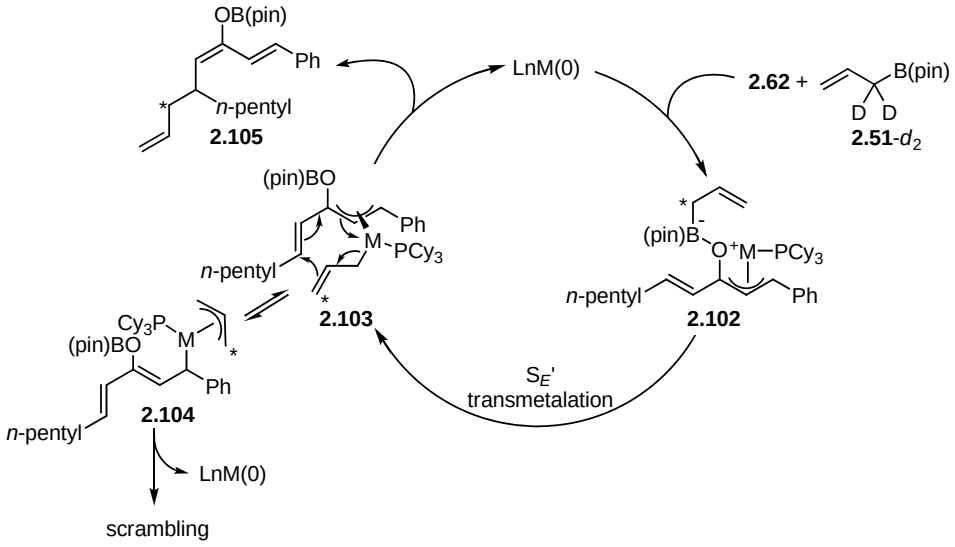
[44] (a) Hayashi, T.; Konishi, M.; Kumada, M. *J. Chem. Soc. Chem. Commun.* **1983**, 736. (b) Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 1279. (c) Hiyama, T.; Matsuhashi, H.; Fujita, A.; Tanaka, M.; Hirabayashi, K.; Shimizu, M.; Mori, A. *Organometallics* **1996**, *15*, 5762. (d) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 704.

[45] See page 333.

Scheme 2.21: Deuterium Labeling Experiments



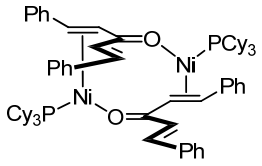
Scheme 2.22: Possible Explanation for Labeling Experiments



Finally, NMR investigations of mixtures of dba, $Ni(cod)_2$, and PCy_3 in THF-d_8 revealed that a new complex formed that had incorporated both dba and PCy_3. Analysis of the ^{31}P NMR spectrum revealed that only one phosphine was ligated to the metal

center even in the presence of excess PCy_3: when 2.0 equiv of PCy_3 was used, relative to dba and $Ni(cod)_2$, a new peak in the ^{31}P NMR spectrum was observed at 38 ppm; in addition to this new peak, free PCy_3 was also present, with the integration between these two peaks being ~1:1. Importantly, only singlets were observed in the ^{31}P NMR spectrum. No evidence for a $(PCy_3)_2Ni$-adduct was observed. Furthermore, integration of the ^{1}H NMR spectrum when using a 1:1:1 mixture of $Ni:PCy_3$:dba was consistent with only one olefin of dba binding to the Ni-center in this complex. These observations may be explained by invoking the existence of dimeric Ni-complex **2.106** (Figure 2.4). While concrete evidence for such a structure by X-ray crystallography could not be obtained, similar (phosphine)Ni(enone) dimers have been isolated by Kurosawa.[46] Further evidence for dimeric Ni-catalysts was found while studying the enantioselective version of this reaction. These results are discussed in section IV.C (page 143).

Figure 2.4: Proposed $[(PCy_3)Ni(dba)]_2$ Dimer



2.106

[46] Ogoshi, S.; Nagata, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 5350.

IV. Development of a Transition-Metal-Catalyzed Asymmetric Conjugate Allylation with Allylboronate Ester Nucleophiles[31b]

A. Discovery of a Competent Chiral Catalyst

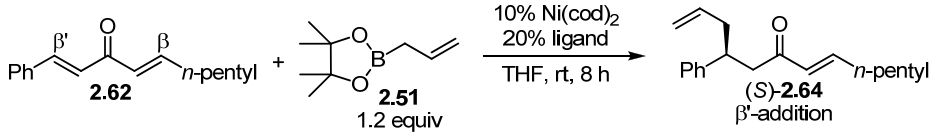
With a better understanding of this new conjugate allylation obtained from our studies of the non-enantioselective reaction, our focus changed to finding a general chiral catalyst that would affect both a chemoselective and an enantioselective conjugate allylation. Chiral TADDOL[47]-derived phosphoramidites, phosphites, and phosphonites (see Figure 2.5) were initially examined as ligands in the reaction when $Ni(cod)_2$ was used as the metal precatalyst. The results of this study are shown in Table 2.4.

Using (TADDOL)MONOPHOS[48] (**2.107**) as the chiral ligand, or other phosphoramidites bearing the TADDOL scaffold, the conjugate allylation product was obtained in moderate yield and poor enantioselectivity (entries 1-3). Interestingly, all of the TADDOL-derived ligands examined gave preferential allylation to the benzylidene site in **2.62** rather than the alkylidene site as was observed in the non-enantioselective reaction. Modification of the TADDOL backbone by substitution at the 3,5-positions of the phenyl ring did lead to improvements in selectivity. Xylyl-substituted TADDOL phosphoramidite **2.110** gave excellent chemoselectivity in the reaction; however, the enantioselectivity was not acceptable (entry 4). Installing larger 3,5-di-*t*-butylphenyl groups on the TADDOL backbone led to an improvement in enantioselectivity (entry 5, 69% ee). Since chemoselectivity and yield were low with this ligand, other 3,5-di-*t*-

[47] Review: Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem. Int. Ed.* **2001**, *42*, 92.
[48] (a) Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron Asymm.* **1998**, *9*, 2409. (b) Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Manganey, P. *Tetrahedron Lett.* **1998**, *39*, 7869.

butylphenyl TADDOL ligands were examined (entries 6-8). Gratifyingly, phosphonite **2.114** affected the conjugate allylation in excellent chemoselectivity, good yield, and high enantioselectivity (entry 8, 88% ee). Other TADDOL-derived phosphonites were inferior to **2.114** in the asymmetric allylation (entries 9 and 10).

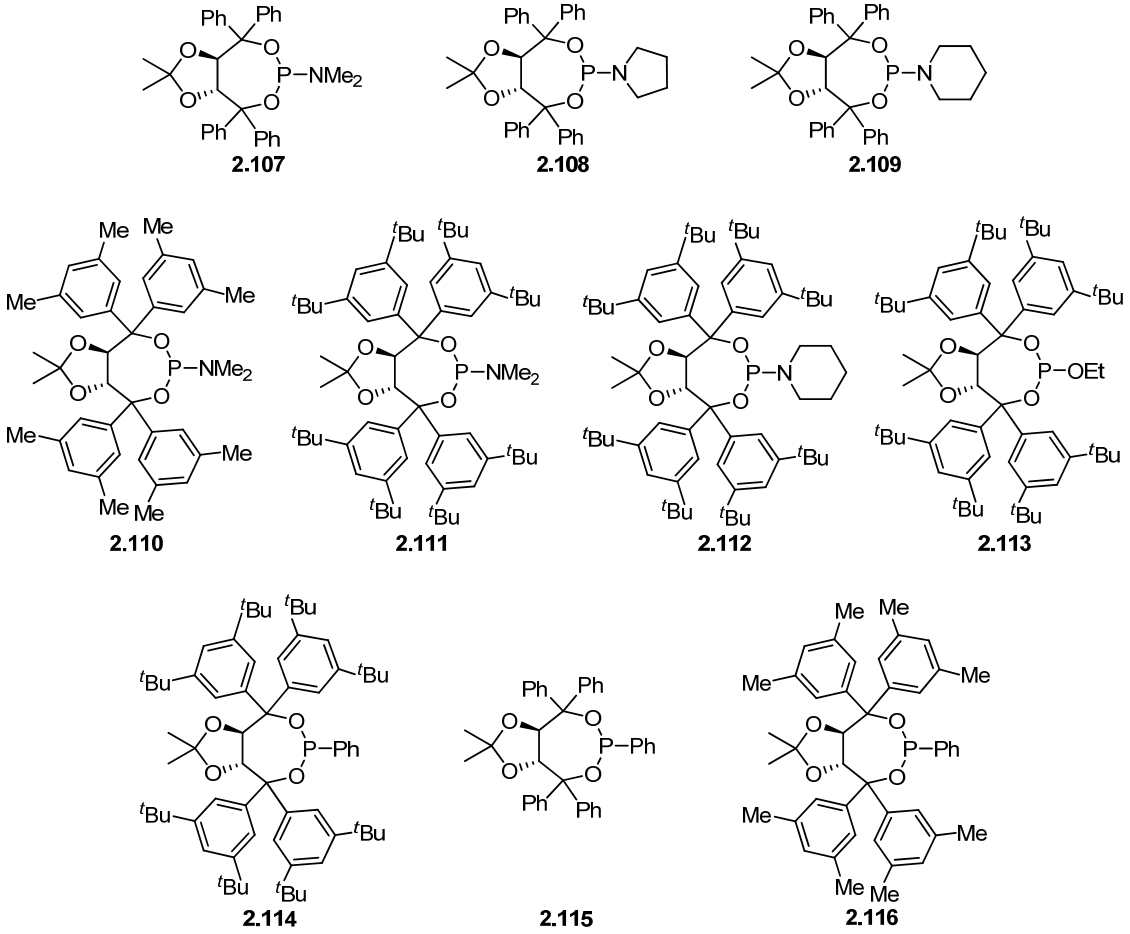
Table 2.4: Survey of Chiral Ligands in the Conjugate Allylation



entry	Ligand[a]	β:β′ [b]	% yield[c]	% ee[d,e]
1	**2.107**	1:3.8	36	44 (75)
2	**2.108**	1:4.3	31	14 (26)
3	**2.109**	1:2.2	57	-2 (84)
4	**2.110**	1:≥20	53	44
5	**2.111**	1:4.7	29	69 (0)
6	**2.112**	1:2.5	24	47 (1)
7	**2.113**	1:16	62	-3
8	**2.114**	1:20	69	88
9	**2.115**	1:3.6	49	28 (81)
10	**2.116**	1:≥20	50	-15

[a]See Figure 2.5 for ligand structures. [b]Value determined by ^{1}H NMR analysis of the unpurified reaction mixture. [c]Isolated yield after silica gel chromatography. Isolated as a mixture of constitutional isomers. [d]Value represents that of the major isomer. [e]Value in parentheses represents that of the minor constitutional isomer.

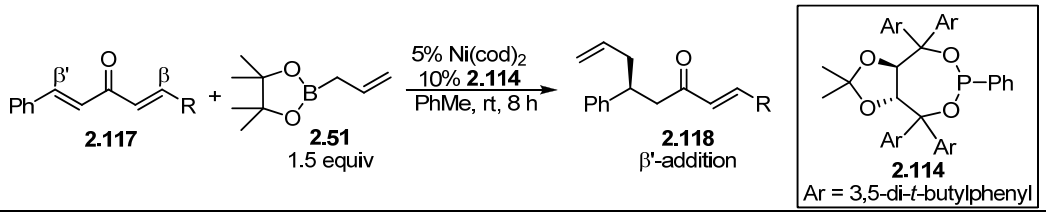
Figure 2.5: Chiral Ligands Used in the Chiral Catalyst Survey



Upon identification of a chiral catalyst for asymmetric conjugate allylation, reaction parameters were optimized in order to reduce catalyst loading and maximize yield and selectivity. The catalyst loading could be reduced to 5% $Ni(cod)_2$ and 10% **2.114** when conducting the reaction at 0.5 M concentration relative to substrate. Furthermore, the enantioselectivity could be increased to 93% ee by using toluene as the reaction solvent instead of THF.

Based on the mechanistic paradigm discussed in section III.D (page 121), it is likely that the nature of the substituent on the activating alkene may affect reaction selectivity. That is, since oxidative addition of the catalyst is proposed to occur at the activating alkene, interaction between the coordination sphere of the metal and the substituents on this alkene may be important for controlling the facial selectivity of the reaction. Therefore, the alkyl substituent on the activating alkylidene unit of the substrate was modified to determine if this group affected reaction selectivity. Furthermore, smaller groups would be more efficient in terms of atom economy. The results of this investigation are shown in Table 2.5. A dramatic effect on chemoselectivity and enantioselectivity was observed. When the substituent of the alkylidene unit was small, higher chemoselectivites were obtained, but suboptimal enantioselectivities prohibited the use of these groups (entries 2 and 3). The larger cyclohexyl group increased enantioselectivity, but chemoselectivity decreased (entry 4). Thus, the *n*-pentyl group afforded the best combination of high chemoselectivity and enantioselectivity.

Table 2.5: Optimization of the Activating Alkene in the DAK Substrate



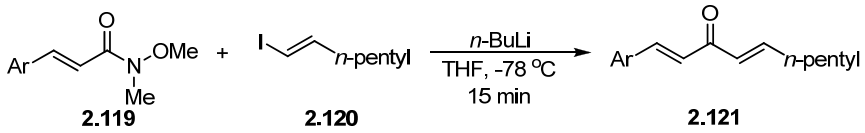
entry	R	β:β′ [a]	% yield[b]	% ee[c]
1	*n*-pentyl	1:17	77	93
2	Me	1:≥20	60	67
3	Et	1:≥20	82	83
4	Cy	1:7	76	96

[a]Value determined by ^{1}H NMR (entries 2-4) or GLC (entry 1) analysis of the unpurified reaction mixture. [b]Isolated yield after silica gel chromatography. Isolated as a mixture of constitutional isomers. [c]Value represents that of the major isomer.

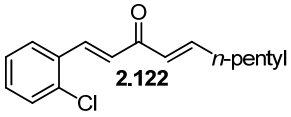
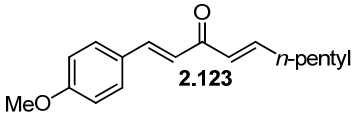
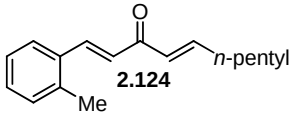
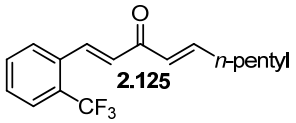
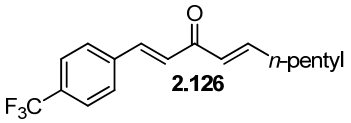
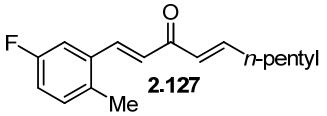
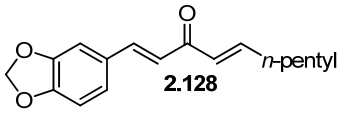
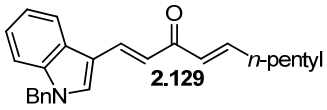
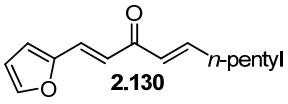
B. Scope and Utility in the Ni-Catalyzed Asymmetric Conjugate Allylation

With the conditions for the asymmetric conjugate allylation optimized, the scope of the reaction was analyzed. Unsymmetrical dialkylidene ketones, all having a heptylidene unit as the activating group, were prepared in good yield using the Weinreb[32] amide ketone synthesis (**2.121**). Results for the syntheses of these substrates are given in Table 2.6.

Table 2.6: Synthesis of Unsymmetrical Dialkylidene Ketones

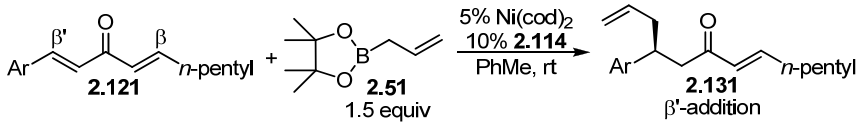


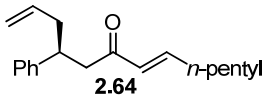
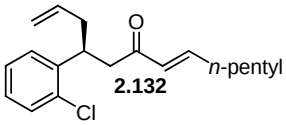
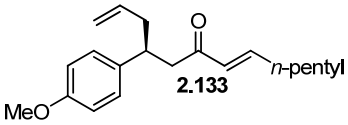
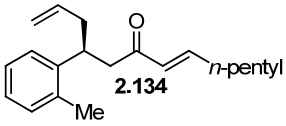
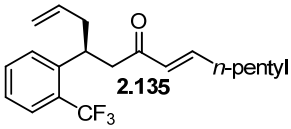
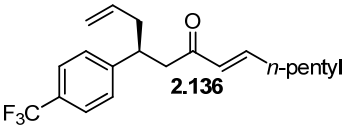
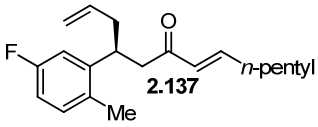
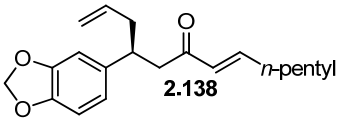
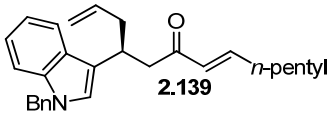
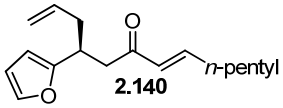
2.119 **2.120** **2.121**

entry	product	% yield
1	 **2.122**	73
2	 **2.123**	90
3	 **2.124**	89
4	 **2.125**	79
5	 **2.126**	66
6	 **2.127**	82
7	 **2.128**	87
8	 **2.129**	88
9	 **2.130**	86

The scope of the asymmetric conjugate allylation is given in Table 2.7. Notably, in all cases, high enantioselectivity was obtained regardless of the aryl substituent of the substrate. Electron-deficient arenes were efficient in terms of reaction rate; however, chemoselectivity was lower for these substrates (entries 2 and 6). Electron-rich arenes reacted slower, and therefore, required longer reaction times; however, chemoselectivities were better for these substrates (entries 3, 8, and 9). Substitution at the *ortho* position of the substrate dramatically increased the chemoselectivity, but allylation was slower with these substrates (entries 4, 5 and 7). In addition, substrates bearing functionalized aromatic groups common in natural products and drug targets were effective in the reaction (entries 8 and 9).

Table 2.7: Substrate Scope in the Asymmetric Conjugate Allylation

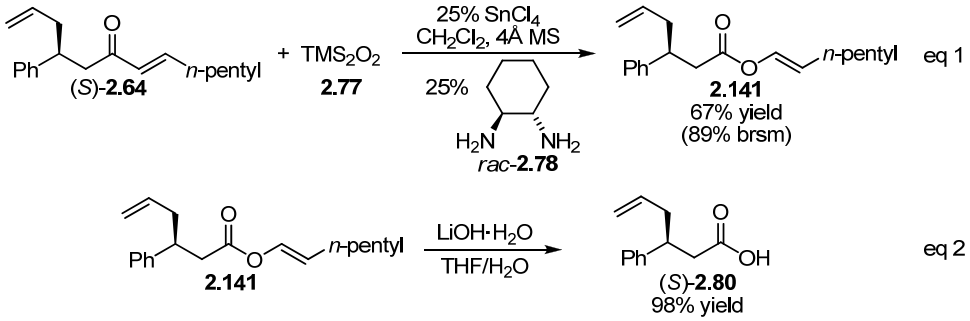


entry	product	time (h)	β′:β[a]	% yield[b]	% ee
1	 2.64	7	17:1	77	93
2	 2.132	7	6.5:1	81	93
3	 2.133	12	20:1	66	91
4	 2.134	12	>20:1	66	93
5	 2.135	48	32:1	45	94
6	 2.136	7	7.0:1	78	94
7	 2.137	12	49:1	81	92
8	 2.138	12	21:1	60	92
9	 2.139	12	>20:1	74	92
10	 2.140	12	5.1:1	52	93

[a]Value determined by ^{1}H NMR (entries 4 and 9) or GLC (entries 1-3, 5-8, and 10) analysis of the unpurified reaction mixture. [b]Isolated yield after silica gel chromatography. Value is an average of at least 2 experiments in each case.

The activating heptylidene unit required for the asymmetric conjugate allylation could be cleaved using the Sn-catalyzed Baeyer-Villiger oxidation[34] described previously (Scheme 2.23, eq 1). Saponification of the resultant ester afforded enantiomerically enriched carboxylic acid **2.80** in near quantitative yield.

Scheme 2.23: Cleavage of the Alkylidene Activating Unit



To further demonstrate the utility of the asymmetric conjugate allylation reaction, this methodology was applied to the synthesis of aminoguanidine **2.148** (Scheme 2.24). Aminoguanidine **2.148** was recently identified as a potent inhibitor of integral plasma membrane proteins that control intracellular pH through Na^+/H^+ exchange (NHE) across the cell membrane.[49] Such targets are potentially useful drugs for the treatment of ischemia-reperfusion injuries. Starting from conjugate allylation product **2.137**, ring-closing metathesis (RCM) afforded cyclic enone **2.142** in excellent yield. The synthesis of enantiomerically enriched 5-substituted cyclohexenones, analogous to **2.142**, via this process (i.e. conjugate allylation followed by RCM) is notable since these compounds are

[49] Fukumoto, S.; Imamiya, E.; Kusumoto, K.; Fujiwara, S.; Watanabe, T.; Shiraishi, M. *J. Med. Chem.* **2002**, *45*, 3009.

useful synthetic building blocks that can be difficult to prepare by other routes.[50] Subsequent α-iodination[51] furnished α-iodoketone **2.143**. An α,β-unsaturated hydrazone side-chain was then introduced via Stille-coupling[52] between **2.143** and stannane **2.144** to produce **2.145**. Finally, a one-pot sequence[53] involving thermal olefin isomerization, followed by electrocyclization, and elimination of dimethylamine afforded pyridine **2.146** in modest isolated yield. In addition to **2.146**, a side-product was isolated and tentatively assigned as quinoline **2.147** from its ^{1}H NMR spectrum.[54] The ratio of **2.146**:**2.147** was ~2:1 as determined from the ^{1}H NMR spectrum of the unpurified reaction mixture. Further optimization of the reaction conditions (solvent, concentration, temperature) did not suppress the formation of this side-product. At this point, the synthesis of **2.146** constituted a formal synthesis of **2.148**. To complete the synthesis, the aminoguanidine functional group was introduced according to the literature.[49]

---

[50] Asymmetric synthesis of 5-substituted cyclohexenones is typically achieved by kinetic resolution. See: Chen, Q.; Kuriyama, M.; Soeta, T.; Hao, X.; Yamada, K. –I.; Tomioka, K. *Org. Lett.* **2005**, *7*, 4439.

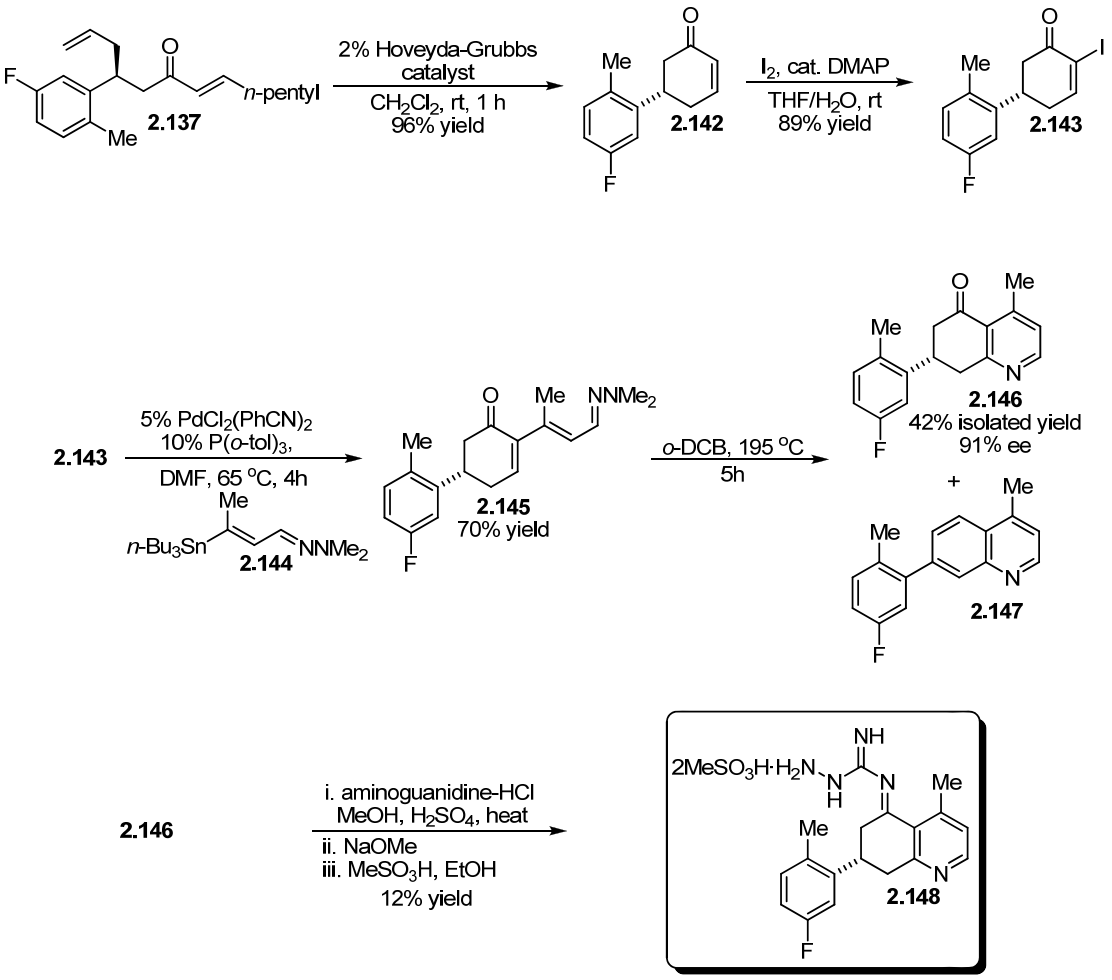
[51] Krafft, M. E.; Cran, J. W. *Synlett* **2005**, *8*, 1263.

[52] For Pd-catalyzed couplings to α-iodoenones, see: (a) Sirisoma, N. S.; Johnson, C. R. *Tetrahedron Lett.* **1998**, *39*, 2059. (b) Johnson, C. R.; Adams, J. P.; Collins, M. A. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1. (c) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayaka, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919. (d) Ruel, F. S.; Braun, M. P.; Johnson, C. R. *Org. Synth.* **1998**, *75*, 69. (e) Banks, J. C.; Van Mele, D.; Frost, C. G. *Tetrahedron Lett.* **2006**, *47*, 2863. (f) Negishi, E.-I. *J. Organomet. Chem.* **1999**, *576*, 179.

[53] (a) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991. (b) Hosokawa, T.; Shimo, N.; Maeda, K.; Sonoda, A.; Murahashi, S.-I.; *Tetrahedron Lett.* **1976**, 383. (c) Verboom, W.; Van Eijk, P. J. S. S.; Conti, P. G. M.; Reinhoudt, D. N. *Tetrahedron* **1989**, *45*, 3131. (d) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumua, S. *J. Org. Chem.* **2001**, *66*, 3099.

[54] Rigorous characterization of **2.147** was not performed.

Scheme 2.24: Synthesis of a Potent NHE Inhibitor



C. Mechanistic Aspects of the Ni-Catalyzed Asymmetric Conjugate Allylation

The effect of ligand enantiomeric purity on selectivity in the conjugate allylation was examined to determine if a linear correlation would result.[55] Significantly, a slight negative non-linear effect was observed (Figure 2.6). Furthermore, the chemoselectivity

[55] For reviews of non-linear effects in asymmetric catalysis, see: (a) Kagan, H. B. *Adv. Synth. Catal.* **2001**, *343*, 227. (b) Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402.

of the reaction was also affected by the enantiomeric purity of the ligand. That is, when racemic ligand was employed in the conjugate allylation, the highest chemoselectivity was observed (27:1 β′:β). In addition, the reaction using racemic catalyst was slightly faster than the conjugate allylation employing ligand of >99% ee (Figure 2.7). Clearly, heterochiral complexes form in the conjugate allylation reaction when the ligand enantiomeric purity is not 100%.

Figure 2.6: Effect of Ligand Enantiomeric Purity on Reaction Selectivity

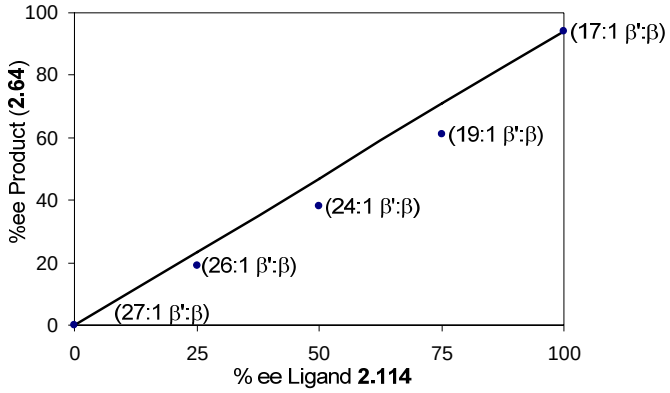
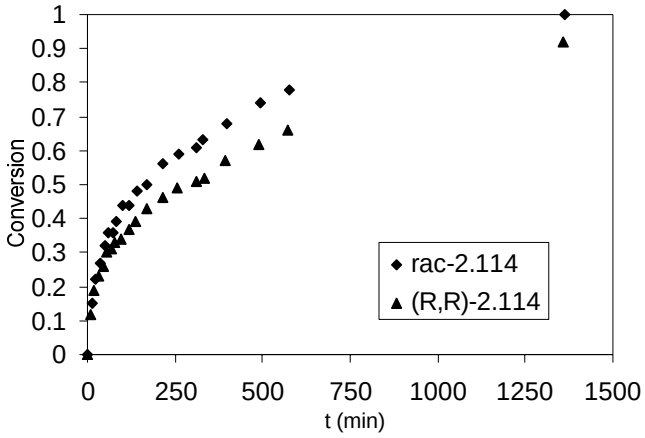


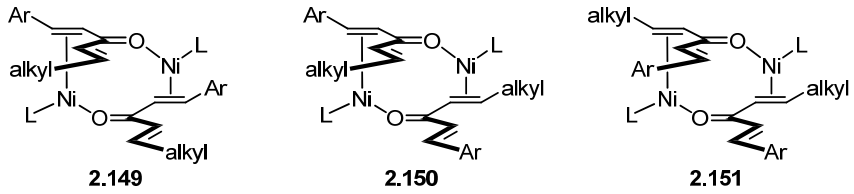
Figure 2.7: Effect of Ligand Enantiomeric Purity on Reaction Rate



Since Pd has been shown to bind two phosphines when coordinated to dba,[56] formation of a (substrate)ML_2 complex during the reaction could explain these results. However, ^{31}P NMR analysis of a 1:1:1 and a 1:2:1 mixture of $Ni(cod)_2$, chiral ligand **2.114**, and dba in C_6D_6 showed the presence of mostly free ligand (156.8 ppm), with a small, new singlet resonance at 166.0 ppm. No evidence for a ML_2 complex was observed. Therefore, a more likely explanation is the formation of [(**2.114**)Ni(substrate)]$_2$ dimers (Figure 2.8) analogous to [(PCy_3)Ni(dba)]$_2$ (**2.106**) described in section III.D (Figure 2.4, page 132). When **2.114** is used in varying enantiomeric purities, either **2.51** induced oxidative addition or dimer dissociation occurs at different rates and with different chemoselectivities for the heterochiral versus homochiral dimeric complexes shown in Figure 2.8. This rate difference produces a non-linear effect.

[56] (a) Amatore, C.; Jutland, A. *Coord. Chem. Rev.* **1998**, *178-180*, 511. (b) Amatore, C.; Jutland, A.; Meyer, G. *Inorg. Chim. Acta.* **1998**, *273*, 76. (c) Amatore, C.; Jutland, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168.

Figure 2.8: Proposed Dimeric Complexes in the Asymmetric Conjugate Allylation

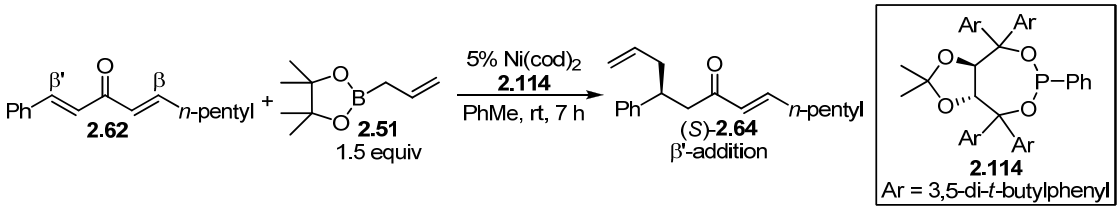


2.149 **2.150** **2.151**

The effect of the metal:ligand ratio was next analyzed for the asymmetric conjugate allylation (Table 2.8). In the absence of ligand, the reaction was quite sluggish, and substantial amounts of the 1,2-addition product was observed (entry 1). In addition, exclusive conjugate allylation to the alkylidene unit of **2.62** was observed when using $Ni(cod)_2$ as catalyst alone. Addition of 0.5 equivalents of ligand relative to metal was enough to favor conjugate allylation over 1,2-allylation of **2.62** (entry 2). Furthermore, the addition of ligand caused a reversal in chemoselectivity, favoring the benzylidene allylation product in a 6.6:1 ratio. Notably, pronounced ligand acceleration[57] was observed considering that high conversion and enantioselection was obtained even in the excess of free $Ni(cod)_2$ relative to ligand. Addition of one equivalent of ligand relative to metal increased conversion, chemoselectivity, and enantioselectivity, while addition of excess ligand relative to metal did not offer any improvements.

[57] Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1995**, *34*, 1059.

Table 2.8: Effect of Metal:Ligand Ratio in the Conjugate Allylation

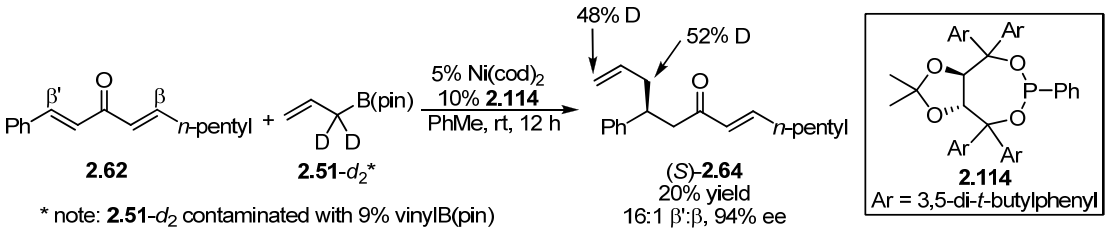


entry	mol% ligand	1,4:1,2[a]	β′:β[b]	% conv[c]	% yield[d]	% ee[e]
1	0	1:1.4	1:>50	38	25	n/a
2	2.5	5:1	6.6:1	82	59	95 (22)
3	5	>20:1	17:1	>95	69	95 (60)
4	7.5	>20:1	17:1	>95	80	94 (86)
5	10	>20:1	17:1	>95	77	93 (87)

[a]Value determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b]Value determined by GLC analysis of the unpurified reaction mixture. [c]Value represents the ratio of **2.64**:**2.62** in the ^{1}H NMR spectrum. [d]Combined yield of 1,2- and 1,4-addition products after silica gel chromatography. [e]Value for the major isomer; number in parentheses represents the value for the minor constitutional isomer.

Deuterium labeling experiments were performed employing the chiral catalyst used in the asymmetric conjugate allylation and **2.51**-d_2 (Scheme 2.25). As was observed in the conjugate allylation of **2.62** with **2.51**-d_2 using $Ni(cod)_2/PCy_3$ as catalyst, deuterium scrambling was also observed in the asymmetric conjugate allylation. Thus η^1-η^3-η^1 allyl isomerization is likely faster than reductive elimination with the chiral catalyst as discussed in section III.D (Scheme 2.22, page 131).

Scheme 2.25: Deuterium Labeling Experiments



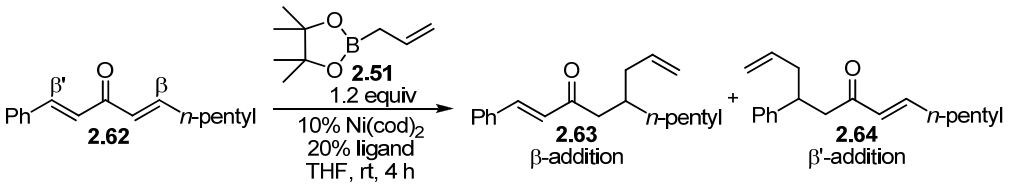
D. Model for Chemoselectivity in the Conjugate Allylation

Using the chemoselectivity data obtained for the ligand surveys in both the enantioselective and non-enantioselective conjugate allylation reaction, a working model for chemoselectivity was developed. Displayed in Table 2.9 is a summary of this data, giving the correlation between ligand basicity and chemoselectivity in the conjugate allylation. The CO stretching frequencies for the *trans*-(ligand)$_2$Rh(CO)Cl complex prepared from each ligand was used as a gauge of ligand basicity.[58] When achiral ligands were employed, chemoselectivity was dependent on the Lewis basicity of the achiral ligand. That is, as the Lewis basicity of the ligand decreased, the chemoselectivity decreased (entries 1-5). Use of highly Lewis basic PCy_3 gave the highest chemoselectivity for alkylidene allylation (entry 1). Furthermore, ligand size did not have a significant affect when using achiral phosphine ligands (entries 4 and 5). Tri(*ortho*-*tert*-butylphenyl)phosphite and triphenylphosphite gave comparable levels of chemoselectivity, yet the Tolman cone angle for P(O-2-^{t}BuPh)$_3$ is significantly larger

[58] (a) Vastag, S.; Heil, B.; Markó, L. *J. Mol. Cat.* **1979**, *5*, 189. (b) Ohgomori, Y.; Yoshida, S.-I.; Watanabe, Y. *J. Chem. Soc., Dalton Trans.* **1987**, 2969. (c) Otto, S.; Roodt, A. *Inorg. Chim. Acta* **2004**, *357*, 1. (d) Fernández, E.; Ruiz, A.; Claver, C.; Castillón, S.; Polo, A. *Organometallics* **1998**, *17*, 2857. (e) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**¸*129*, 8766.

relative to $P(OPh)_3$ (175° vs 128°, respectively).[59] However, as can be noted in entries 4 and 5 (Table 2.9), these ligands still fit the ligand basicity trend. Interestingly, TADDOL-derived chiral phosphines did not fit this Lewis basicity trend (entry 6). The electronic nature of TADDOL-derived phosphoramidite **2.110** is similar to PPh_3, yet very high chemoselectivity was realized using this ligand relative to PPh_3, which was relatively non-selective (entry 3 vs 6). Presumably, there is a steric preference with the chiral ligand, which leads to this enhanced chemoselectivity. Since achiral ligands do not appear to effect chemoselectivity based on sterics, the chirality of the TADDOL backbone has a dramatic effect on chemoselectivity that cannot be explained by simple cone angle arguments.

Table 2.9: Correlation Between Ligand Basicity and Chemoselectivity



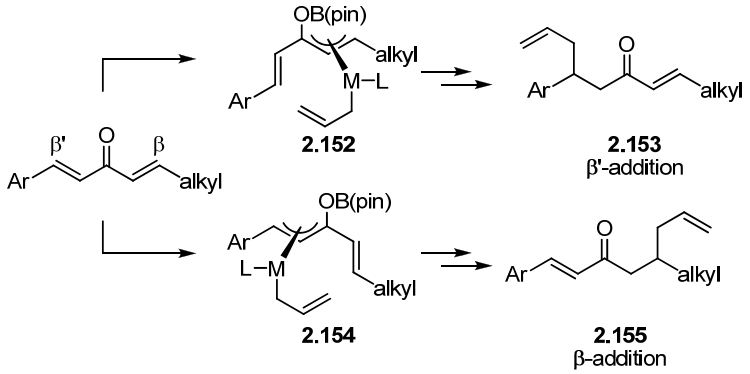
entry	ligand	ν_{CO} (cm^{-1})[a]	β′:β	% yield
1	PCy_3	1943	1:7.5	82
2	$P(NMe_2)_3$	1964	1:2.5	82
3	PPh_3	1979	1:2.4	49
4	$P(O\text{-}2\text{-}^tBuPh)_3$	2012	1:1.5	40
5	$P(OPh)_3$	2016	1:1.1	55
6	**2.110**	1984	>20:1	53

[a]These values represent that of the *trans*-$L_2Rh(CO)Cl$ complex. See footnote 58.

[59] Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

The above observations can best be accommodated by considering the stability of the π-allyl complexes (**2.152** vs **2.154**, Scheme 2.26). This argument assumes that π-allyl stability is product-determining. In support of this hypothesis, electron-rich metals, where the π-allyl bearing the electron-withdrawing aryl ring should be favored (**2.154**), lead to the alkylidene allylation product via [3,3′]-reductive elimination. This was the observed reaction outcome using Lewis basic PCy_3. Furthermore, steric analysis of **2.152** and **2.154** predicts that when the alkyl group is small, **2.152** should predominate to minimize steric interactions with the ligand (L). While this was not observed for achiral ligands, TADDOL-derived phosphines appear to effect chemoselectivity based on this steric preference, and therefore, afford arylidene allylation. As was observed during optimization of the substrate (Table 2.5, page 137), increasing the size of the alkyl group led to decreased chemoselectivity for arylidene allylation. This result supports a steric model when using chiral TADDOL-derived phosphonite **2.114**. Moreover, the substrate scope study for the asymmetric conjugate allylation revealed that smaller aryl groups led to decreased chemoselectivity (Table 2.7, entry 1 vs 10, page 140). In addition, *ortho*-substitution on the aryl group of the substrate led to increased chemoselectivity in the reaction (Table 2.7, entry 1 vs 4, 5, and 7). These observations are consistent with a steric argument grounded on π-allyl complex stability.

Scheme 2.26: Model for Chemoselectivity in the Conjugate Allylation



While the chemoselectivity in the asymmetric conjugate allylation always favors arylidene allylation, subtle changes in the electronic nature of the arylidene unit of the substrate affected chemoselectivity. Arguably, dπ-π* donation from the metal to the aryl-ring of the substrate, similar to the dba-effect[60] recognized in cross-coupling reactions, may add to the stabilization of **2.154**. Thus, when the aryl group of the substrate is electron-withdrawing, this dπ-π* donation should be enhanced, leading to more alkylidene allylation. The reverse should be true for electron-rich aryl groups, and this trend was observed in the conjugate allylation: when substrates with electron-withdrawing substituents on the aryl ring were used in the asymmetric conjugate allylation, lower chemoselectivities were obtained (i.e. more alkylidene allylation, Table 2.7, entry 1 vs 2 and 6, page 140). Likewise, substrates bearing electron-donating substituents on the aryl ring gave more arylidene allylation (Table 2.7, entry 1 vs 3 and 8).

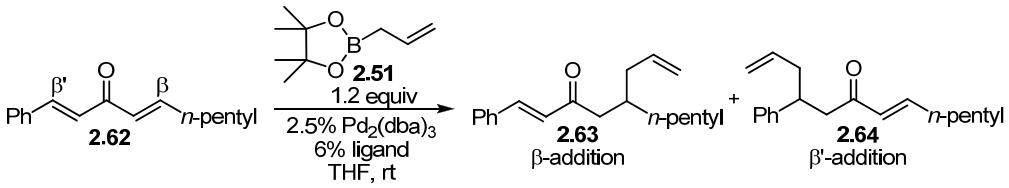
[60] (a) Mace, Y.; Kapdi, A. R.; Fairlamb, J. S.; Jutand, A. *Organometallics* **2006**, *25*, 1795. (b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435.

In summary, for achiral ligands, the Lewis basicity appears to control chemoselectivity in the allylation. However, with chiral TADDOL-derived ligands, sterics appear to be more significant in controlling chemoselectivity.

E. Extension to an Asymmetric Chemoselective Alkylidene Conjugate Allylation

The general asymmetric conjugate allylation described in Table 2.7 (page 140) provides a solution for asymmetric conjugate allylation to furnish benzylic stereocenters; however, formation of aliphatic stereocenters is also desirable. Because of the difference in reactivity observed with Pd vs Ni-catalysts, various chiral TADDOL-derived phosphine ligands were examined, using $Pd_2(dba)_3$ as the precatalyst, with the goal of developing an asymmetric alkylidene conjugate allylation (Table 2.10). Modification of the amino moiety of the ligand did not improve enantioselectivity (entries 1-3); however, modification of the TADDOL-backbone led to increased enantioselectivities (entries 4 and 5). While this survey did identify a chiral catalyst that afforded the alkylidene allylation product in excellent enantiomeric purity (entry 5), no catalyst system gave useful levels of chemoselectivity for alkylidene allylation. In fact, as observed under Ni-catalysis, chiral Pd-catalysts bearing TADDOL-derived phosphine ligands generally favored arylidene allylation.

Table 2.10: Chiral Catalyst Survey with $Pd_2(dba)_3$ as Precatalyst



entry	ligand[a]	β:β′ [b]	% yield[c]	% ee[d]
1	**2.107**	1:3.4	76	25 (12)
2	**2.108**	1:26	66	-14 (8)
3	**2.109**	1:3.4	63	38 (25)
4	**2.110**	1:2	80	79 (32)
5	**2.111**	1.6:1	74	96 (33)
6	**2.112**	1:17	68	83 (2)
7	**2.113**	1:7.8	82	39 (19)
8	**2.114**	1:11	74	46 (16)

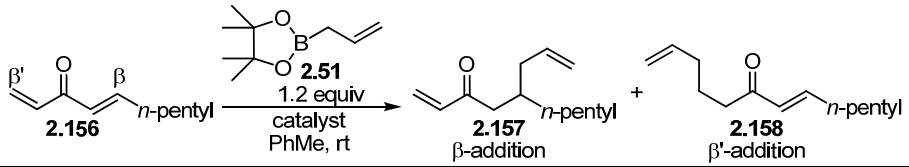
[a]See Figure 2.5 for ligand structures (page 135). [b]Value determined by ^{1}H NMR analysis of the unpurified reaction mixture. [c]Isolated yield after silica gel chromatography. Isolated as a mixture of constitutional isomers [d]Value for the β-isomer, value in parentheses represents that of the β′-isomer.

To solve this chemoselectivity issue, it was reasoned that the aryl-group in **2.62** could be used to control chemoselectivity in the conjugate allylation. This strategy was based on the chemoselectivity model discussed in section IV.D (page 148). Since smaller aryl groups should increase alkylidene allylation, we reasoned that replacement of the phenyl ring in **2.62** with a proton should allow for maximum alkylidene allylation. Therefore, **2.156** was prepared (using carbonylative Stille-coupling[61]) and surveyed in the conjugate allylation (Table 2.11). Under Ni-catalysis, good chemoselectivity could

[61] Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, s. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417.

be obtained in some cases; however, enantioselectivity was never of acceptable quality (entries 1-5). Interestingly, the chiral catalyst developed for the asymmetric arylidene conjugate allylation gave only modest enantioselectivity (entry 1). The use of Pd as catalyst did consistently give high chemoselectivity for the desired constitutional isomer (entries 6-15). TADDOL-derived phosphoramidites proved to be the best ligand class for the reaction with **2.156** (entries 6-10). Again, substitution on the aromatic groups of the TADDOL-scaffold was required for enantioselection. Phosphoramidites with 3,5-disubstituted phenyl groups on the TADDOL backbone all gave higher enantioselectivities relative to the parent phenyl compound (compare entries 6 and 7 with entries 8-12). Furthermore, phosphonites (entries 12-14) and phosphites (entry 15) were inferior in the conjugate allylation of **2.156**. It was clear from these results that a new ligand structure was needed for successful allylation of **2.156** with high enantioselection.

Table 2.11: Chiral Catalyst Survey with 2.156 as Substrate



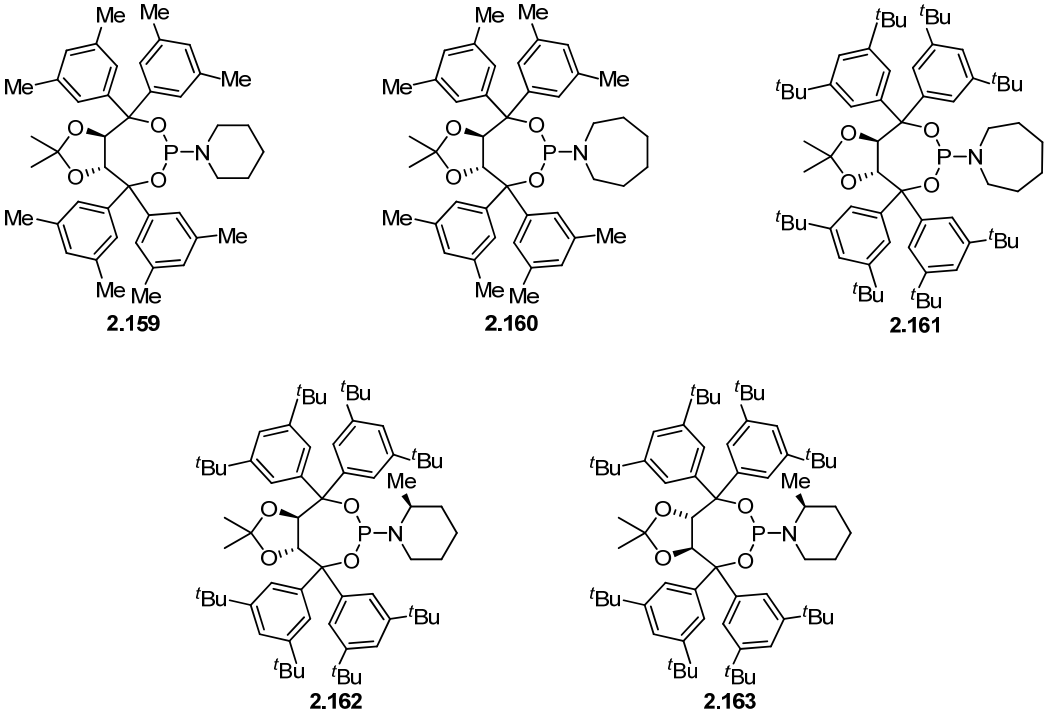
entry	metal	ligand[a]	β:β′ [b]	% yield[c]	% ee
1	5% $Ni(cod)_2$	10% **2.114**	14:1	21	54
2	5% $Ni(cod)_2$	10% **2.115**	9:1	31	45
3	5% $Ni(cod)_2$	10% **2.111**	2.4:1	32	1
4	5% $Ni(cod)_2$	10% **2.112**	1.5:1	44	0
5	5% $Ni(cod)_2$	10% **2.113**	0:1	n.d.	n/a
6	2.5% $Pd_2(dba)_3$	6% **2.107**	15:1	45	-7
7	2.5% $Pd_2(dba)_3$	6% **2.109**	19:1	38	9
8	2.5% $Pd_2(dba)_3$	6% **2.110**	11:1	3	-47
9	2.5% $Pd_2(dba)_3$	6% **2.111**	20:1	15	32
10	2.5% $Pd_2(dba)_3$	6% **2.112**	35:1	10	50
12	2.5% $Pd_2(dba)_3$	6% **2.115**	22:1	43	2
13	2.5% $Pd_2(dba)_3$	6% **2.116**	17:1	38	-41
14	2.5% $Pd_2(dba)_3$	6% **2.114**	17:1	22	-5
15	2.5% $Pd_2(dba)_3$	6% **2.113**	32:1	1	-8

[a]See Figure 2.5 for ligand structures (page 135). [b]Value determined by GLC analysis of the unpurified reaction mixture. [c]Isolated yield after silica gel chromatography. Isolated as a mixture of constitutional isomers.

From the data displayed in Table 2.11, it was determined that TADDOL-derived phosphoramidites, containing 3,5-disubstitiuted aryl rings on the TADDOL backbone, were promising ligands and should be explored further. In addition, an increase in enantioselectivity was observed with increasing size of the amino moiety of the

phosphoramidite (Table 2.11, entries 9 and 10). Therefore, the TADDOL-derived phosphoramidite ligands in Figure 2.9 were synthesized to find a competent chiral ligand for this transformation. These phosphoramidite ligands were rationally designed to possess sterically more demanding amino groups.

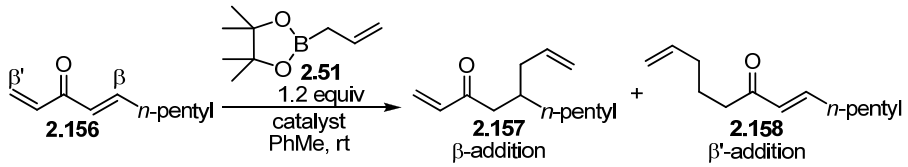
Figure 2.9: New Ligands for Asymmetric Alkylidene Allylation



The results for the conjugate allylation of **2.156** when using these newly prepared ligands are tabulated in Table 2.12. When increasing the size of the amino moiety on the phosphoramidite from a 6- to 7-membered heterocycle, little improvement was observed in the enantioselectivity; however, chemoselectivity improved dramatically (Table 2.12: compare entries 1 and 2, and compare Table 2.11, entry 10 with Table 2.12, entry 3).

Gratifyingly, introduction of a methyl group onto the heterocycle (**2.162**) provided a solution (Table 2.12, entry 4). Thus in the presence of phosphoramidite **2.162**, the conjugate allylation of **2.156** proceeded in excellent enantioselectivity and chemoselectivity in modest yield. Furthermore, the opposite diastereomer of ligand (**2.163**) was the mismatched case, affording the conjugate allylation product in excellent chemoselectivity, but with poor enantioselectivity (entry 5).

Table 2.12: Chiral Catalyst Survey with Newly Prepared Phosphoramidites



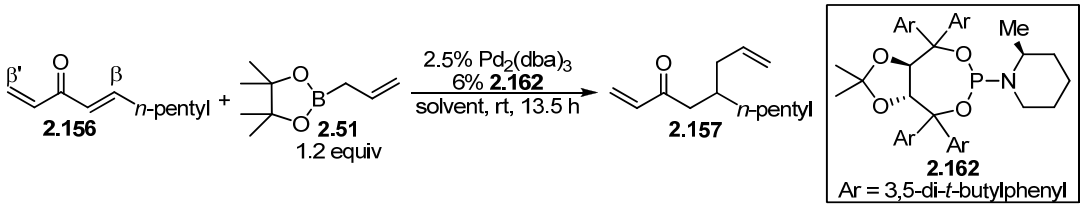
entry	metal	ligand[a]	β:β′ [b]	% yield[c]	% ee
1	2.5% $Pd_2(dba)_3$	6% **2.159**	14:1	16	-29
2	2.5% $Pd_2(dba)_3$	6% **2.160**	21:1	7	-24
3	2.5% $Pd_2(dba)_3$	6% **2.161**	63:1	50	52
4	2.5% $Pd_2(dba)_3$	6% **2.162**	>50:1	39	86
5	2.5% $Pd_2(dba)_3$	6% **2.163**	>50:1	47	-44

[a]See Figure 2.9 for ligand structures (page 156). [b]Value determined by GLC analysis of the unpurified reaction mixture. [c]Isolated yield after silica gel chromatography. Isolated as a mixture of constitutional isomers.

With a chiral catalyst identified for alkylidene conjugate allylation, a short solvent screen was conducted to determine if enantioselection could be enhanced (Table 2.13). Etheral solvents were better in terms of chemical yield; however, all solvents examined

gave comparable levels of enantioselection. THF was determined to be the best choice of solvent for the reaction.

Table 2.13: Solvent Effects in the Asymmetric Conjugate Allylation of 2.156



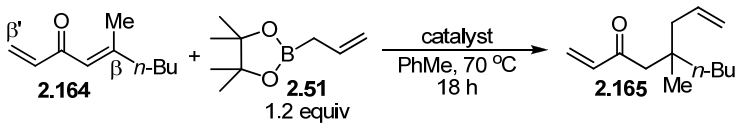
entry	solvent	β:β′ [a]	% yield[b]	% ee
1	THF	>50:1	52	86
2	Et_2O	>50:1	48	87
3	*t*-BuOMe	>50:1	41	85
4	*o*-DCB	>50:1	42	84

[a]Value determined by GLC analysis of the unpurified reaction mixture. [b]Isolated yield after purification by silica gel chromatography.

After successfully developing a catalyst for chemoselective alkylidene allylation, a method for the formation of all-carbon quaternary stereocenters was sought. Initially, **2.164** was prepared and examined in the conjugate allylation (Table 2.14). Unfortunately, when employing the ligand identified for the asymmetric allylation of **2.156** in the conjugate allylation of **2.164**, only modest enantioselectivity was obtained in conjunction with poor conversion (entry 1). Increasing the reaction temperature to 70 ^{o}C did not improve reaction efficiency (entry 2). Furthermore, the use of other phosphoramidites, under Pd-catalysis, also gave both poor conversion and

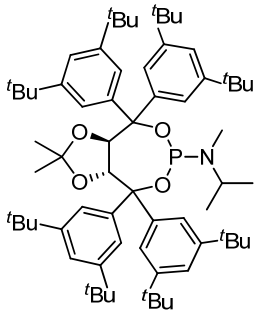
enantioselectivity (entries 3-6). Conversion was slightly better with phosphoramidites containing smaller amino moieties (entries 4 and 5); however, this led to decreased enantioselectivities. Moreover, a phosphite bearing a bulky *t*-butyl group also gave poor conversion and enantioselectivity (entry 7). Increasing the reaction temperature and/or time in these reactions did not increase reaction conversion and often gave unidentified side-products. Interestingly, use of the chiral Ni-catalyst developed for the asymmetric arylidene allylation gave high conversion, but substantial amounts of the undesired constitutional isomer (entry 8).

Table 2.14: Attempts at Formation of All-Carbon Quaternary Stereocenters

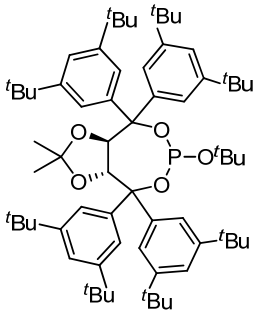


entry	metal	ligand	% conv[a]	β:β′ [a]	% ee
1[b]	2.5% $Pd_2(dba)_3$	6% **2.162**[c]	2	>50:1	73
2	2.5% $Pd_2(dba)_3$	6% **2.162**[c]	9	>50:1	63
3	2.5% $Pd_2(dba)_3$	6% **2.163**[c]	6	>50:1	-33
4	2.5% $Pd_2(dba)_3$	6% **2.110**[d]	15	>50:1	-13
5	2.5% $Pd_2(dba)_3$	6% **2.111**[d]	18	>50:1	33
6	2.5% $Pd_2(dba)_3$	6% **2.166**	7	>50:1	51
7	2.5% $Pd_2(dba)_3$	6% **2.167**	14	>50:1	-27
8	5% $Ni(cod)_2$	10% **2.114**[d]	98	1:6.7	50

[a]Value determined by GLC analysis of the unpurified reaction mixture. [b]Reaction run at rt for 24 h. [c]See Figure 2.9 (page 156). [d]See Figure 2.5 (page 135).



2.166

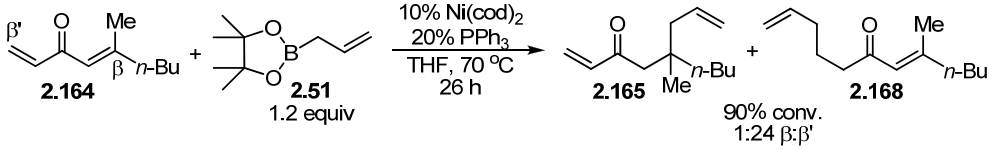


2.167

Further analysis of the conjugate allylation with **2.164** showed that Ni-catalysts were more active than their Pd counterparts, giving high conversion (Scheme 2.27). Unfortunately, the undesired constitutional isomer was formed as the major product in high chemoselectivity. Assuming that oxidative addition (π-allyl formation) occurs to the less hindered β′-site of **2.164**, it is likely that direct reductive elimination to the β′-

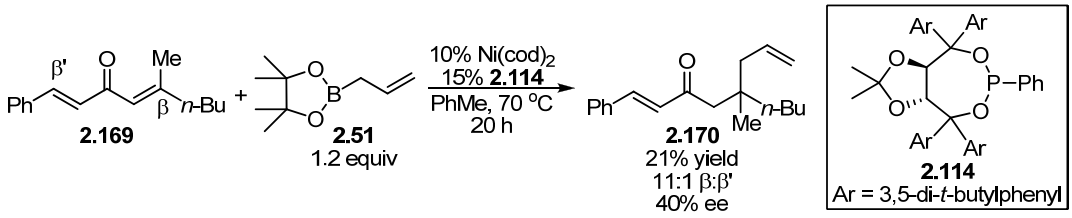
position is now competitive with [3,3′]-reductive elimination to the β-position. Rate enhancement that is typically provided by [3,3′]-reductive elimination is likely lost because of the steric hindrance associated with forming an all-carbon quaternary stereocenter. Supporting the hypothesis that direct reductive elimination may occur, is the observation that simple alkylboron reagents have been used as nucleophiles in the conjugate addition of acrylates under Ni(0) catalysis.[24a]

Scheme 2.27: Reaction of 2.164 with $Ni(cod)_2/PPh_3$



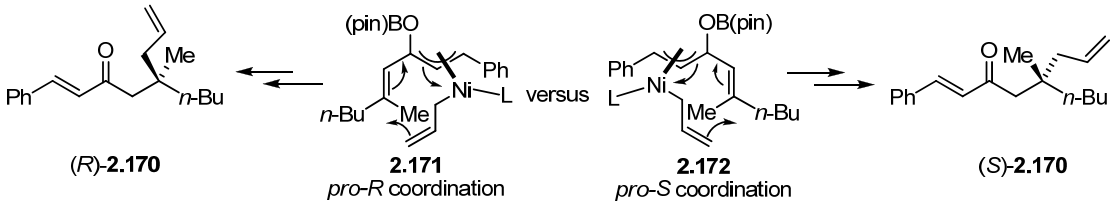
To solve this chemoselectivity issue when using Ni as the catalyst, it was considered that reintroduction of the aryl group in the dialkylidene ketone substrate may slow down direct reductive elimination and allow for [3,3′]-reductive elimination to be competitive again. Bolstering this idea, was the observation that Ni/PCy_3 gave chemoselective conjugate allylation to form an all-carbon quaternary center when **2.72** was used as substrate (Table 2.3, entry 8, page 120). Thus, **2.169** was prepared and analyzed as a substrate for asymmetric conjugate allylation (Scheme 2.28). While chemoselectivity did improve when using **2.169** as substrate, both isolated yield and enantioselectivity were poor.

Scheme 2.28: Attempts at an Asymmetric Conjugate Allylation of 2.169



An important observation in the conjugate allylation of **2.169** was that the trisubstituted olefin of the recovered starting material had isomerized under the reaction conditions. Based on our understanding of this conjugate allylation process, we had hoped that quaternary stereocenters bearing groups of similar size could be prepared in high enantioselectivity. That is to say, successful asymmetric conjugate allylation of **2.169** would formally result from differentiation of a methyl and a butyl group by a chiral catalyst. Since these groups are similar in size, such a process is difficult. However, it is possible that the chiral catalyst dictates which enantiotopic face of the intermediate π-allyl it will bind (i.e. **2.171** vs **2.172**, Scheme 2.29). If this is the case, and the [3,3′]-reductive elimination is stereospecific, then the activating alkene of the substrate should dictate the enantioselectivity in the reaction and not the substituents adjacent to the carbon being allylated. If this contention is accurate, then the geometry of the trisubstituted olefin in **2.169** should control which enantiomer is formed in the conjugate allylation. *Thus, a chiral catalyst for successful asymmetric conjugate allylation of **2.169** must not isomerize the trisubstituted olefin during the conjugate allylation.*

Scheme 2.29: Possible Mode of Asymmetric Induction in the Conjugate Allylation



In an attempt to increase the rate of conjugate allylation relative to starting material isomerization, the reaction in Scheme 2.28 was performed using 3.0 equiv of **2.51** at 1 M concentration relative to **2.169**. Isomerization of recovered **2.169** was less in this case (~5:1); however, **2.170** was isolated in only 31% yield, 9:1 chemoselectivity, and 45% ee. Furthermore, improvement in conversion, as evident by ^{1}H NMR analysis of the unpurified reaction mixture, was not observed despite the slight increase in yield. If enantioselectivity in the reaction is controlled by the model given in Scheme 2.29, then one would predict that **2.170** should be obtained in ~86% ee. This conclusion is based on the enantiomeric purity of the alkylidene allylation product resulting from allylation of **2.62** when using Ni(cod)$_2$/**2.114** as catalyst (Table 2.8, entry 4, page 147). This is clearly not the case in the above example, even when alkene isomerization in **2.169** had been reduced. The difference in temperature between the present reaction and the asymmetric allylation of **2.62**, given in Table 2.8, may be the result for this discrepancy. However, this has yet to be determined since the allylation reaction of **2.169** does not proceed at room temperature when Ni(cod)$_2$ and **2.114** are employed. Another possible explanation

is that steric interaction between the methyl group of the substrate and the allyl ligand of the metal result in lower enantioselectivity.

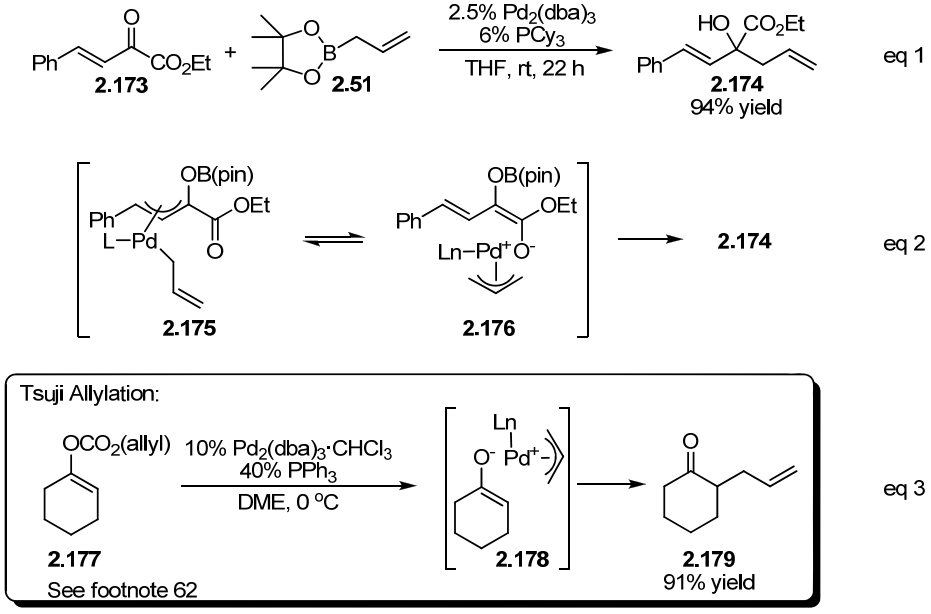
The formation of all-carbon quaternary stereocenters via asymmetric conjugate allylation remains an unsolved problem. From the experiments discussed above, it is likely that a catalyst system which affects conjugate allylation at room temperature may be required in order to achieve high enantioselectivities. No chiral Pd or Ni catalysts prepared from chiral TADDOL-derived phosphonites, phosphoramidites, or phosphites were found to form quaternary stereocenters at room temperature. However, because the activating olefin in the substrate can be used as a tuning element, the addition of electron withdrawing substituents on the phenyl ring in **2.169** may further lower the barrier for reductive elimination by withdrawing electron density from the metal center. This may allow the conjugate allylation to proceed at reduced temperatures. Application of this strategy has not been carried out; therefore, its relevance is pure conjecture at this point.

F. Other Related Reactions

As discussed in section III.A (page 113), typical unsaturated electrophiles (Figure 2.1, page 115) were inert to the catalytic conjugate allylation described herein. However, another class of α,β-unsaturated electrophiles that were found to be reactive were α,β-unsaturated α-ketoesters (**2.173**, Scheme 2.30). Surprisingly, these substrates gave complete 1,2-addition (eq 1). While it was not determined why these substrates reacted in a 1,2-fashion, rather than the expected 1,4-sense, it is likely that these substrates can

react analogously to the well known Tsuji-allylation (Scheme 2.30, eq 3).[62] In the Tsuji reaction, allyl enol carbonate **2.177** is converted to α-allylcyclohexanone (**2.179**) via intermediate **2.178**. In an analogous manner, the bis(allyl)Pd complex **2.175** (eq 2), in the allylation of **2.173**, may be in equilibrium with Pd-enolate complex **2.176**, which is remarkably similar to **2.178**. Reductive elimination at the α-carbon of the extended ester enolate offers a rationale for the production of **2.174**.

Scheme 2.30: Use of an α,β-Unsaturated α-Ketoesters

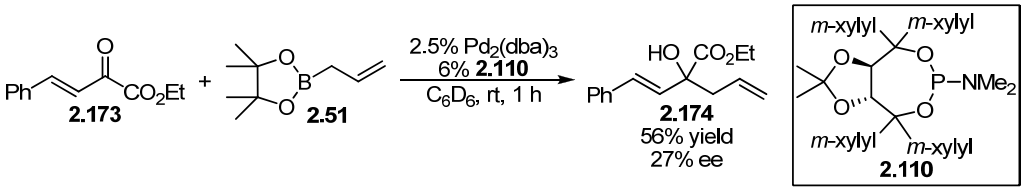


Importantly, the 1,2-addition product of **2.173** was not derived from background reaction between **2.173** and **2.51**: control experiments verified that both metal and phosphine ligand were required for successful allylation. Further, performing the

[62] (a) Tsuji, J.; Minami, I.; Shimizu, S. *Tetrahedron Lett.* **1983**, *24*, 1793. (b) Minami, I.; Nisar, M.; Yuhara, M.; Shimizu, I.; Tsuji, J. *Synthesis* **1987**, 992.

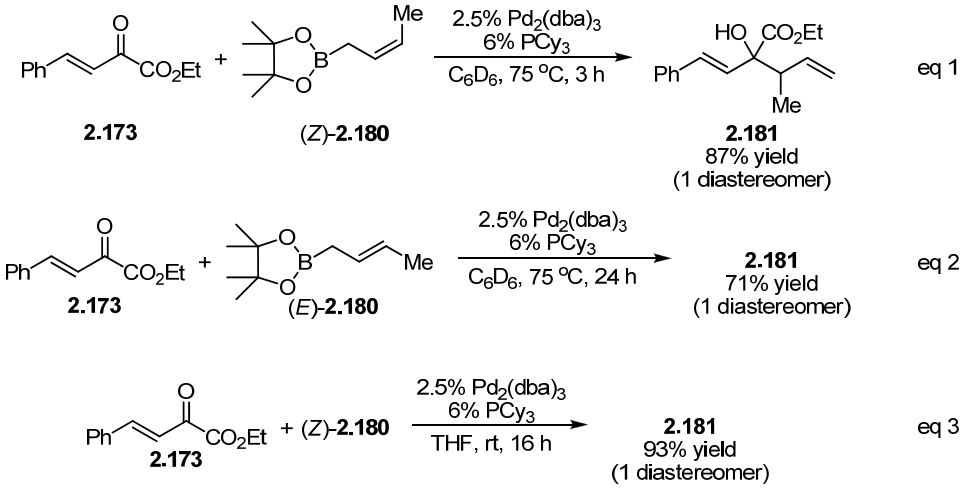
allylation in the presence of chiral phosphoramidite ligand **2.110** led to formation of **2.174** in good yield with some enantiocontrol (Scheme 2.31).

Scheme 2.31: Enantioselective Allylation of 2.173



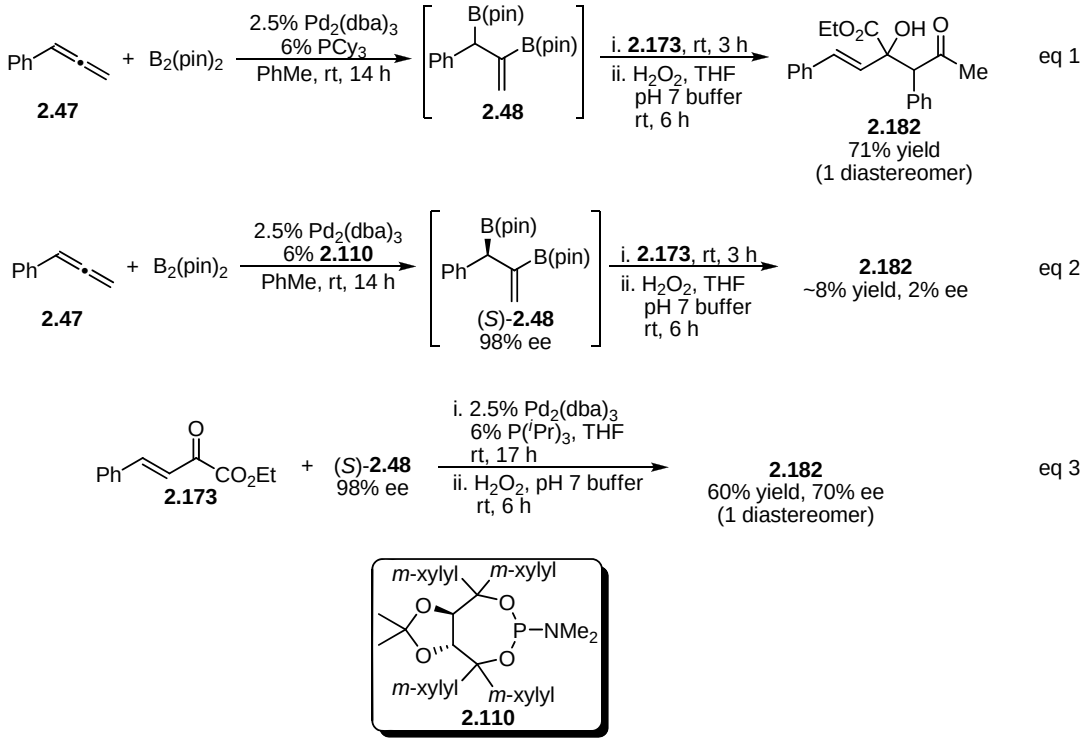
In addition to allylation, crotylation of **2.173** was also successful using Pd-catalysis (Scheme 2.32). The use of *Z*-configured crotylboronate **2.180** led to the γ-crotylation product **2.181** as a single diastereomer in good yield (eq 1). The use of the *E*-configured crotylboronate led to the same diastereomer of product; however, much longer reaction time was needed (eq 2). Interestingly, the use of THF as solvent provided a dramatic increase in rate, allowing for the crotylation to be performed at room temperature with excellent yield (eq 3). It should be noted that aliphatic α,β-unsaturated α-ketoesters were not allylated or crotylated under the reaction conditions described here. Competitive β-hydride elimination appeared to be problematic when these electrophiles were used.

Scheme 2.32: Catalytic Crotylation of 2.173



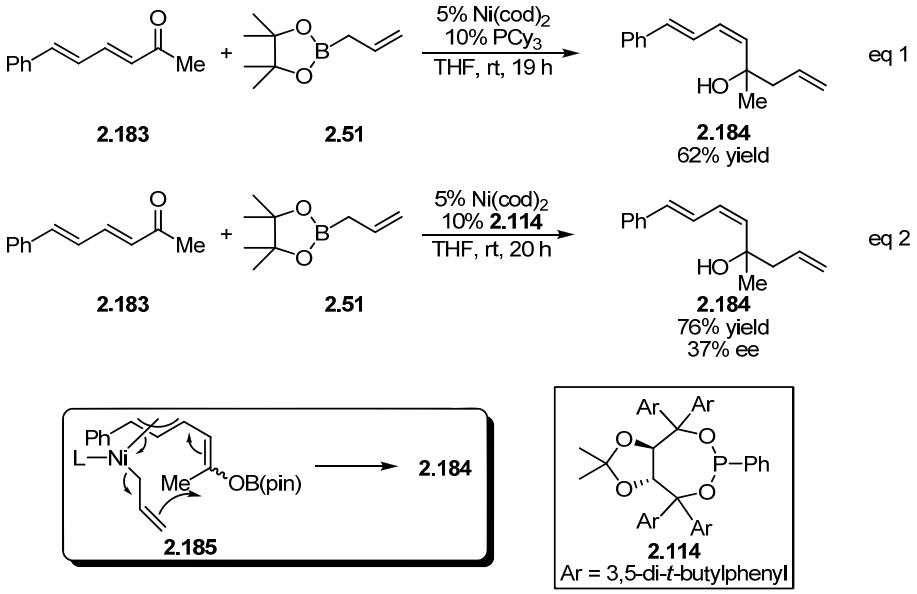
Similar to crotylboronates, the allene diboration products participated in the catalytic allylation of **2.173** (Scheme 2.33). A one-pot tandem diboration/allylation/oxidation gave **2.182** as a single diastereomer in good yield (eq 1). Again, 1,2-addition to **2.173** was observed. Interestingly, when the same sequence was performed using the optimal chiral ligand for the asymmetric allene diboration, very little of the allylation/oxidation product was isolated (eq 2). Furthermore, no enantioinduction was observed. However, treatment of **2.173** with purified, enantiopure **2.48**, using $Pd_2(dba)_3/P(^iPr)_3$ as the catalyst in the allylation, gave good yield of **2.182**, after oxidation, with moderate chirality transfer (eq 3). Clearly, this suggests that the chirality of the enantiomerically pure catalyst in eq 2 is mismatched with the chirality of **2.48** in the subsequent catalytic allylation. Thus, a tandem one-pot diboration/allylation process could not be developed.

Scheme 2.33: Catalytic Addition of a Diboronate Esters to 2.173



Finally, in addition to unsaturated α-ketoesters, α,β,γ,δ-unsaturated enone **2.183** also underwent allylation under Ni-catalysis (Scheme 2.34). Due to the fact that the (*E,Z*)-diene (**2.184**) was isolated as the reaction product, this class of substrates arguably reacts through a [3,3′]-reductive elimination pathway (**2.185**) to arrive at the observed product. Use of a chiral TADDOL-derived phosphonite afforded the allylation product in modest enantioselectivity, verifying the involvement of the chiral catalyst.

Scheme 2.34: Catalytic Allylation of an α,β,γ,δ-Unsaturated Enone



V. Conclusions

The discovery and development of a transition-metal-catalyzed asymmetric conjugate allylation has been reported. The following insights have been gained from this research:

1. Allylboronate nucleophiles readily add to the β-position of dialkylidene ketones when group 10 transition metals are used as catalysts. Furthermore, this reactivity is unique to dialkylidene ketones. This enhancement of reactivity is postulated to occur due to a facile [3,3′]-reductive elimination pathway that can operate for this class of substrates, which is not accessible to other α,β-unsaturated electrophiles.
2. Under Ni(0)-catalysis, the use of Lewis basic ligands leads to chemoselective conjugate allylation to the alkylidene site in unsymmetrical dialkylidene ketones,

while the use of chiral TADDOL-derived ligands affords chemoselective and enantioselective arylidene allylation.

3. The alkyl and aryl groups on the activating alkene in unsymmetrical dialkylidene ketones can be used as a control element to affect both chemoselectivity and enantioselectivity.
4. A catalytic asymmetric conjugate allylation that affords enantiomerically enriched conjugate allylation products from arylidene or alkylidene allylation has been described.
5. The conjugate allylation products can be further manipulated into valuable organic synthons.
6. Formation of all-carbon quaternary stereocenters via conjugate allylation is feasible; however, a competent chiral catalyst has not been found.
7. An α,β-unsaturated α-ketoester and an α,β,γ,δ-unsaturated enone also participate in allylation reactions with allylboronates under group 10 metal catalysis. These electrophiles afford 1,2-allylation products rather than 1,4-allylation products.

VI. Experimental Procedures

A. General. Melting points were determined using a Mel-Temp II melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Inova-500 (500 MHz), Gemini-400 (400 MHz), Unity-300 (300 MHz), or Bruker DRX 300 or 400 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the residual solvent resonance as an internal standard ($CHCl_3$: 7.24 ppm, C_6HD_5: 7.15 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Bruker DRX 400 (100 MHz) instrument, a Gemini-400 (100 MHz) instrument, or an Inova-500 (125 MHz) instrument with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.0 ppm, C_6D_6: 128.39 ppm). ^{19}F NMR spectra were recorded on an Inova-500 (470 MHz) instrument. Chemical shifts are reported in ppm and are referenced to a 0.05% solution of C_6F_6 (-63.72 ppm) in C_6D_6. ^{31}P NMR spectra were recorded on a Unity-300 (121 MHz), a Bruker 400 MHz (161 MHz), or an Inova-500 (202 MHz) instrument with complete proton decoupling. Chemical shifts are reported in ppm and are referenced to 85% H_3PO_4 (0.0 ppm). Low-resolution mass spectrometry was performed by the University of North Carolina, Department of Chemistry Mass Spectrometry Facility and by the Boston College, Department of Chemistry Mass Spectrometry Facility. Infrared (IR) spectra were obtained on Nicolet 210 or 560 spectrophotometer. Optical rotations were measured using a Rudolf Research Analytical Autopol IV Polarimeter.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 40-63 μm) purchased from Silicycle. Thin layer chromatography (TLC) was performed on 250 μm silica gel plates from Silicycle or 200 μm neutral alumnia TLC plates from Sorbent Technologies. Visualization was achieved using UV light, phosphomolybdic acid in ethanol, potassium permanganate in water, or cerium(IV) sulfate and ammonium molybdate in sulfuric acid, each followed by heating.

Analytical chiral gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 series chromatograph equipped with a CTC Analysis Combi Pal autosampler by Leap Technologies (Carrboro, NC), a split mode capillary injection system, a flame ionization detector, and a Supelco β-dex 120 column with helium as the carrier gas. The inlet pressure and split ratio were 25 psi and 35, respectively, in all cases unless otherwise noted. Analytical achiral GLC was performed on a Hewlett-Packard 6890 series chromatograph equipped with a split mode capillary injection system, a flame ionization detector, and a Hewlett-Packard Ultra 1 capillary column (0.33 μm film thickness, 25 m length, 0.2mm ID) with helium as the carrier gas. The inlet pressure and split ratio were 25 psi and 15, respectively, in all cases unless otherwise noted. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Berger Instruments supercritical chromatograph equipped with an Alcott autosampler and a Knauer UV detector. Analytical chiral high performance liquid chromatography (HPLC) was performed on a Shimadzu instrument with UV detector.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Toluene, toluene-d_8, and benzene-d_6 were distilled over

CaH_2 and degassed by freeze-pump-thaw cycles prior to use. Anhydrous tetrahydrofuran (THF), used in reactions performed outside a dry-box, was freshly distilled from Na metal and benzophenone or purified using a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. by passing the solvent through two activated alumina columns after being purged with Ar. Anhydrous THF, used in reactions that were prepared in a dry-box, was purchased from Aldrich Chemical Company. Methylene chloride and diethyl ether were purified using a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. by passing the solvent through two activated alumina columns after being purged with Ar.

Tris(dibenzylideneacetone)dipalladium(0) and bis(1,5-cyclooctadiene)nickel(0) were purchased from Strem Chemical Company. Allylboronic acid pinacol ester (**2.51**) was purchased from Aldrich Chemical Company and distilled through a 6 inch Vigreux column (58-62 ^{o}C at 20 torr) and stored in the freezer under Ar. Allenes and allene diboration products were prepared according to the methods described in Chapter 1 (see page 47). 1-Iododheptene was synthesized from 1-heptyne via hydroalumination with DIBAL followed by iodination.[1] 2-Iodovinylcyclohexane and 1-iodo-3,3-dimethyl-1-butene were synthesized via hydroboration of cyclohexylacetylene or *t*-butylacetylene, respectively, followed by iodination.[2] Vinyliodides bearing pendant TBS-protected alcohols were synthesized via hydrozirconation of the TBS-protected propargyl or homo

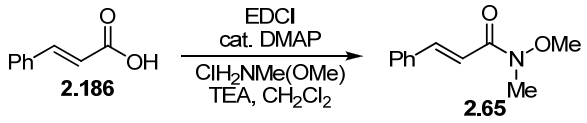
[1] (a) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138. (b)Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 4599.
[2] (a) Brown, H. C.; Hamaoka, T. Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6075. (b)Gagnon, D.; Lauzon, S.; Godbout, C.; Spino, C. *Org. Lett.* **2005**, *7*, 4769.

propargyl alcohol with the Schwartz reagent, followed by iodination.[3] Vinyl bromides were purchased from Aldrich Chemical Company and used without further purification. 5-Fluoro-2-methylbenzaldehyde was purchased from Oakwood Chemicals and used without further purification. All other reagents were purchased from either Fisher or Aldrich Chemical Companies and used directly.

B. Experimental Procedures.

1. Weinreb Amide Syntheses

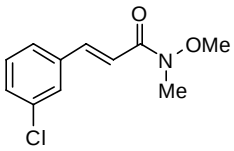
General procedure for synthesis of Weinreb amides:



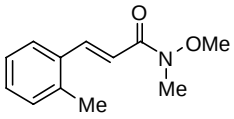
To 11.7 g (79.0 mmol) of *trans*-cinnamic acid (**2.186**) and 11.6 g (119 mmol) of (*N*,*O*)-dimethylhydroxylamine hydrochloride in 316 mL of CH_2Cl_2 in a 1 L round-bottom flask with magnetic stir-bar was added 1.93 g (15.8 mmol) of 4-(dimethylamino)pyridine (DMAP) followed by 22.8 g (119 mmol) of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI), all in one portion. This mixture was put under N_2 and 15.7 mL (12.0 g, 119 mmol) of triethylamine was added dropwise over a 10 min period. After addition, the mixture was allowed to stir overnight at ambient temperature. The final mixture was transferred to a separatory funnel, washed with 3 M HCl (2x) followed by saturated aqueous $NaHCO_3$. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Silica gel chromatography

[3] Germain, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5269.

(hexanes:EtOAc) afforded 13.1 g (68.5 mmol, 87%) of Weinreb amide **2.65** as a white solid. Spectral data were consistent with the literature.[4]

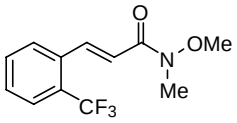


(*E*)-3-(3-Chlorophenyl)-*N*-methoxy-*N*-methylacrylamide (2.187). Prepared according to the general procedure on page 174 in 85% yield. A white solid. Mp 48-52 ^{o}C. R_f = 0.29 (SiO_2, 2:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3069 (m), 2974 (m), 2930 (m), 2823 (m), 1659 (s), 1615 (s), 1564 (s), 1469 (s), 1425 (s), 1389 (s), 1199 (s) (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.62 (1H, d, *J* = 16 Hz), 7.52 (1H, s), 7.34-7.42 (1H, m), 7.22-7.32 (2H, m), 6.99 (1H, d, *J* = 16 Hz), 3.74 (3H, s), 3.27 (3H, s); ^{13}C NMR ($CDCl_3$): δ 166.3, 141.7, 136.9, 134.6, 129.9, 129.6, 127.4, 126.4, 117.1, 61.91, 32.45. LRMS (ESI+) Calcd for $C_{11}H_{12}ClNO_2$ $(M)^+$: 225.1, Found $(M)^+$: 225.6.

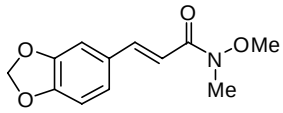


(*E*)-*N*-Methoxy-*N*-methyl-3-*o*-tolylacrylamide (2.188). Prepared according to the general procedure on page 174 in 90% yield. A colorless oil. R_f = 0.35 (SiO_2, 1:1 hexanes:EtOAc); IR (neat): 3062 (w), 2968 (m), 2936 (m), 1659 (s), 1615 (s), 1464 (m), 1413 (m), 1388 (s), 1180 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.99 (1H, d, *J* = 16 Hz), 7.57 (1H, d, *J* = 8.0 Hz), 7.12-7.26 (3H, m), 6.92 (1H, d, *J* = 16 Hz), 3.72 (3H, s), 3.28 (3H, s), 2.41 (3H, s); ^{13}C NMR ($CDCl_3$): δ 166.8, 141.0, 137.5, 134.0, 130.5, 129.4, 126.1, 126.0, 116.8, 61.75, 32.39, 19.76. LRMS (ESI+) Calcd for $C_{12}H_{15}NO_2$ $(M)^+$: 205.1, Found $(M)^+$: 205.6.

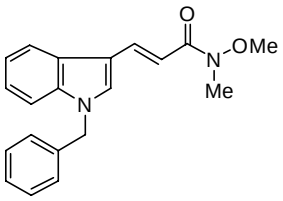
[4] Hiyama, T.; Reddy, G. B.; Minami, T.; Hanamoto, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 350.



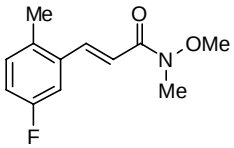
(*E*)-*N*-Methoxy-*N*-methyl-3-[2-(trifluoromethyl)phenyl]acrylamide (2.189). Prepared according to the general procedure on page 174 in 48% yield. A colorless oil. R_f = 0.15 (SiO_2, 3:1 hexanes:EtOAc); IR (neat): 3075 (w), 2974 (m), 2936 (m), 2823 (w), 1841 (w), 1658 (s), 1627 (s), 1488 (s), 1381 (s), 1312 (s), 1287 (s), 1161 (s), 1123 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.06 (1H, app dq, *J* = 16 Hz, *J* = 2.4 Hz), 7.70 (1H, d, *J* = 8.0 Hz), 7.65 (1H, d, *J* = 8.0 Hz), 7.53 (1H, t, *J* = 8.0 Hz), 7.42 (1H, d, *J* = 8.0 Hz), 6.96 (1H, d, *J* = 16 Hz), 3.72 (3H, s), 3.28 (3H, s); ^{13}C NMR ($CDCl_3$): δ 165.9, 138.9, 134.3, 131.9, 129.0, 128.7 (q, $^2J_{CF}$ = 30 Hz), 127.9, 126.0 (q, $^3J_{CF}$ = 5.5 Hz), 123.9 (q, $^1J_{CF}$ = 272 Hz), 120.3, 61.88, 32.42. LRMS (APPI) Calcd for $C_{12}H_{12}F_3NO_2$ $(M + H)^+$: 260.1, Found $(M + H)^+$: 260.1.



(*E*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-methoxy-*N*-methylacrylamide (2.190). Prepared according to the general procedure on page 174 in 57% yield. A white solid. Mp 107-110 °C. R_f = 0.21 (SiO_2, 1:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 2974 (m), 2936 (m), 2905 (m), 1841 (w), 1652 (s), 1614 (s), 1501 (s), 1444 (s), 1375 (s), 1255 (s), 1180 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.59 (1H, d, *J* = 16 Hz), 7.03 (1H, s), 6.99 (1H, d, *J* = 8.0 Hz), 6.81 (1H, d, *J* = 16 Hz), 6.75 (1H, d, *J* = 8 Hz), 5.94 (2H, s), 3.70 (3H, s), 3.25 (3H, s); ^{13}C NMR ($CDCl_3$): δ 166.9, 149.0, 148.0, 142.9, 129.4, 124.0, 113.6, 108.3, 106.4, 101.3, 61.72, 32.44. LRMS (ESI+) Calcd for $C_{12}H_{13}NO_4$ $(M)^+$: 235.1, Found $(M)^+$: 235.6.



(*E*)-3-(1-Benzyl-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacrylamide (2.191). The title compound was prepared by Horner-Wadsworth-Emmons olefination between diethyl(*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate and 1-benzyl-1H-indole-3-carbaldehyde[5] in 86% yield.[6] A white solid. Mp 42-46 ^{o}C. R_f = 0.14 (SiO_2, 2:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3106 (m), 3055 (m), 2968 (m), 2936 (m), 1651 (s), 1608 (s), 1526 (m), 1469 (s), 1381 (s), 1167 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.96 (1H, d, *J* = 16 Hz), 7.90-8.0 (1H, m), 7.40 (1H, s), 7.20-7.34 (6H, m), 7.10 (2H, d, *J* = 6.4 Hz), 7.05 (1H, d, *J* = 16 Hz), 5.26 (2H, s), 3.79 (3H, s), 3.31 (3H, s); ^{13}C NMR ($CDCl_3$): δ 168.1, 137.4, 136.4, 136.2, 132.1, 128.7, 127.8, 126.7, 126.2, 122.8, 121.1, 120.4, 113.0, 110.7, 110.3, 61.59, 50.20, 32.51. LRMS (APPI) Calcd for $C_{20}H_{20}N_2O_2$ $(M + H)^+$: 321.2, Found $(M + H)^+$: 321.2.



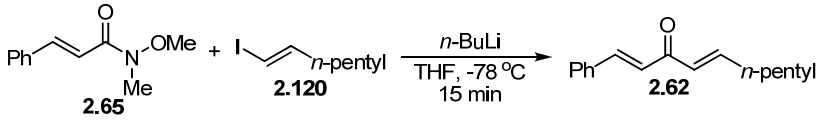
(*E*)-3-(5-Fluoro-2-methylphenyl)-*N*-methoxy-*N*-methylacrylamide (2.192). The title compound was prepared by Horner-Wadsworth-Emmons olefination between diethyl(*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate and 5-fluoro-2-methylbenzaldehyde in 78% yield.[68] A white solid. Mp 68-72 ^{o}C. R_f = 0.14 (SiO_2, 3:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3075 (w), 2973 (m), 2936 (m), 1658 (s), 1620 (s), 1589 (m), 1495 (s), 1412 (m), 1381 (s), 1262 (m), 1179 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.88 (1H, dd, *J* = 16 Hz, *J* = 1.6 Hz), 7.23 (1H, dd, *J* = 9.6 Hz, *J* = 2.4 Hz), 7.10 (1H, dd, *J* = 8.4 Hz, *J* = 5.6 Hz),

[5] Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915.
[6] Netz, D. F.; Seidel, J. L. *Tetrahedron Lett.* **1992**, *33*, 1957.

6.90 (1H, dt, J = 8.4 Hz, J = 2.4 Hz), 6.88 (1H, d, J = 16 Hz), 3.73 (3H, s), 3.27 (3H, s), 2.35 (3H, s); ^{13}C NMR ($CDCl_3$): δ 166.4, 161.1 (d, $^1J_{CF}$ = 242 Hz), 139.9, 135.6 (d, $^3J_{CF}$ = 7.0 Hz), 133.1, 131.9 (d, $^3J_{CF}$ = 7.8 Hz), 117.9, 116.2 (d, $^2J_{CF}$ = 20 Hz), 112.4 (d, $^2J_{CF}$ = 22 Hz), 61.84, 32.41. LRMS (APPI) Calcd for $C_{12}H_{14}FNO_2$ $(M + H)^+$: 224.1, Found $(M + H)^+$: 224.1.

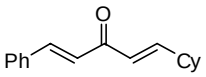
2. Dialkylidene Ketone Syntheses

Synthesis of 2.62

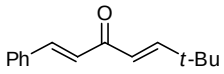


To 2.25 g (10.0 mmol) of (*E*)-1-iodoheptene (**2.120**) in 10 mL of THF at –78 °C was added 4.2 mL (10 mmol) of a 2.4 M solution of *n*-BuLi in hexane dropwise. This solution was allowed to stir for 30 min at –78 °C and then transferred dropwise by canula to a solution of 0.965g (5.00 mmol) of **2.65** in 50 mL of THF at –78 °C. After complete addition (10 min), TLC analysis showed complete consumption of **2.65** after 15 min at –78 °C, so the reaction was subsequently quenched with saturated aqueous NH_4Cl. The unpurified mixture was transferred to a separatory funnel with 1 M HCl and CH_2Cl_2. The organic layer was collected after shaking, and the aqueous layer was extracted with CH_2Cl_2 (1x). The combined organics were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Silica gel chromatography (hexanes/EtOAc) of the

mixture afforded 1.0 g (4.4 mmol, 88%) of (1*E*, 4*E*)-1-phenyldeca-1,4-dien-3-one (**2.62**) as a yellow oil. Spectral data were consistent with the literature.[7]

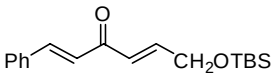


(1*E*,4*E*)-1-Cyclohexyl-5-phenylpenta-1,4-dien-3-one (2.68). Prepared in 96% yield according to the procedure used to synthesize **2.62** on page 178. A yellow solid. Mp 42-46 ^{o}C. R_f = 0.20 (12:1 hexanes:EtOAc); IR (KBr): 2924 (m), 2847 (m), 1806 (w), 1670 (s), 1627 (s), 1592 (s), 1441 (s), 1332 (s), 1278 (m), 1184 (m) cm^{-1}; ^{1}H NMR: δ 7.62 (1H, d, *J* = 16 Hz), 7.55 (2H, m), 6.97 (1H, d, *J* = 164 Hz), 6.93 (1H, dd, *J* = 16 Hz, *J* = 6.8 Hz), 6.37 (1H, dd, *J* = 14 Hz, *J* = 1.2 Hz), 2.19 (1H, m), 1.61-1.88 (5H, m) 1.10-1.40 (5H, m); ^{13}C NMR: δ 189.6, 153.2, 142.8, 134.8, 130.3, 128.9, 128.2, 126.8, 124.8, 40.87, 31.80, 25.90, 25.71. LRMS (ESI+) Calcd for $C_{17}H_{10}O$ $(M + Na)^+$: 263.1, Found $(M + Na)^+$: 263.2.

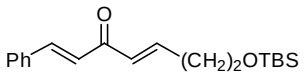


(1*E*,4*E*)-6,6-Dimethyl-1-phenylhepta-1,4-dien-3-one (2.69). Prepared in 86% yield according to the procedure used to synthesize **2.62** on page 178. An off-white solid. Mp 60-64 ^{o}C. R_f = 0.30 (12:1 hexanes:EtOAc); IR (KBr): 3060 (w), 3017 (w), 2948 (m), 2862 (w), 1950 (w), 1880 (w), 1658 (s), 1588 (s), 1449 (m), 1324 (s), 1208 (s), 1165 (s) cm^{-1}; ^{1}H NMR: δ 7.63 (1H, d, *J* = 16 Hz), 7.56 (2H, m), 7.37 (3H, m), 6.71 (1H, d, *J* = 16 Hz), 6.32 (1H, d, *J* = 16 Hz), 1.12 (9H, s); ^{13}C NMR: δ 189.7, 157.9, 142.9, 134.8, 130.3, 128.9, 128.3, 124.9, 124.5, 33.97, 28.72. LRMS (ESI+) Calcd for $C_{15}H_{18}O$ $(M + Na)^+$: 237.1, Found $(M + Na)^+$: 237.1.

[7] Tsuge, O.; Kanemasa, S.; Nakagawa, N.; Suga, H. *Bull. Chem. Soc. Jpn.* **1987**, *69*, 4091.

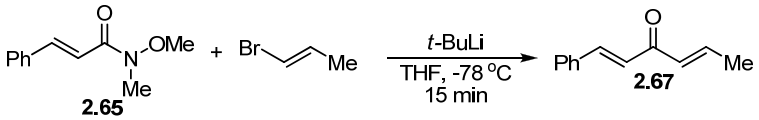


(1*E*,4*E*)-6-(*t*-Butyldimethylsilyloxy)-1-phenylhexa-1,4-dien-3-one (2.70). Prepared in 60% yield according to the procedure used to synthesize **2.62** on page 178. A yellow oil. R_f = 0.20 (12:1 Hexanes:EtOAc); IR (neat): 3060 (w), 2955 (s), 2932 (s), 2854 (s), 1953 (w), 1806 (w), 1666 (s), 1634 (s), 1592 (s), 1449 (s), 1332 (s), 1254 (s), 1138 (s) cm^{-1}; ^1H NMR: δ 7.64 (1H, d, *J* = 16 Hz), 7.56 (2H, m), 7.38 (3H, m), 7.02 (1H, dt, *J* = 15 Hz, *J* = 3.6 Hz), 6.95 (1H, d, *J* = 16 Hz), 6.73 (1H, dt, *J* = 15 Hz, *J* = 2.0 Hz), 4.41 (2H, m), 0.94 (9H, s), 0.10 (6H, s); ^{13}C NMR: δ 189.1, 146.1, 143.4, 134.7, 130.4, 128.9, 128.3, 126.5, 125.3, 62.52, 25.86, 18.37, -5.41. LRMS (ESI+) Calcd for $C_{18}H_{26}O_2Si$ $(M + H)^+$: 303.2, Found $(M + H)^+$: 303.2.

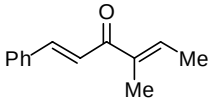


(1*E*,4*E*)-7-(*t*-Butyldimethylsilyloxy)-1-phenylhepta-1,4-dien-3-one (2.71). Prepared in 87% yield according to the procedure used to synthesize **2.62** on page 178. A yellow oil. R_f = 0.19 (12:1 hexanes:EtOAc); IR (neat): 3029 (w), 2952 (s), 2854 (s), 1950 (w), 1802 (w), 1662 (s), 1631 (s), 1596 (s), 1472 (m), 1336 (m), 1254 (s), 1185 (m) cm^{-1}; ^1H NMR: δ 7.63 (1H, d, *J* = 16 Hz), 7.55 (2H, m), 7.38 (3H, m), 6.98 (1H, dt, *J* = 16 Hz, *J* = 8.6 Hz), 6.96 (1H, d, *J* = 16 Hz), 3.61 (1H, dt, *J* = 16 Hz, *J* = 1.2 Hz), 3.76 (2H, t, *J* = 6.4 Hz) 3.08 (2H, dq, *J* = 7.2 Hz, *J* = 1.6 Hz), 0.88 (9H, s), 0.050 (3H, s), 0.042 (3H, s); ^{13}C NMR: δ 189.1, 144.7, 143.1, 134.8, 130.8, 130.3, 128.9, 128.2, 124.6, 61.60, 36.15, 25.86, 18.28, -5.33. LRMS (ESI+) Calcd for $C_{19}H_{28}O_2Si$ $(M + Na)^+$: 339.2, Found $(M + Na)^+$: 339.2.

Synthesis of 2.67



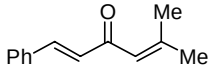
To 1.05 g (8.68 mmol) of (*E*)-1-bromopropene in 16 mL of THF at –78 °C was added 10.8 mL (17.2 mmol) of a 1.6 M solution of *t*-BuLi in pentane dropwise over a 15 min period. This solution was allowed to stir at this temperature for 30 min and then transferred at ~1 drop/s by canula to a solution of 0.832 g (4.35 mmol) of **2.65** in 33 mL of THF at –78 °C (addition of the vinyllithium at faster rates gave lower yields). After complete addition, TLC analysis showed complete consumption of the starting material after 15 min at –78 °C, so the reaction was subsequently quenched with saturated aqueous NH_4Cl. The unpurified mixture was transferred to a separatory funnel with 1 M HCl and Et_2O. The organic layer was collected after shaking, and the aqueous layer was extracted with Et_2O (1x). The combined organics were washed with H_2O, then brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Silica gel chromatography (hexanes/EtOAc) of the mixture afforded 0.571 g (3.32 mmol, 76%) of (1*E*, 4*E*)-1-phenylhexa-1,4-dien-3-one (**2.67**) as a yellow oil. Spectral data were consistent with the literature.[8]



(1*E*,4*E*)-4-Methyl-1-phenylhexa-1,4-dien-3-one (2.73). Prepared in 53% yield according to the procedure used to synthesize **2.67** on page 181. A yellow oil. R_f = 0.19 (14:1 hexanes:EtOAc); IR (neat): 3060 (m), 2920 (m), 1953

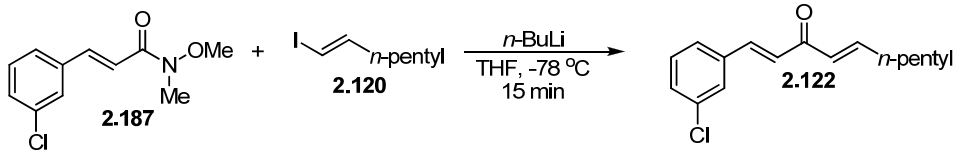
[8] Kubota, K.; Isaka, M.; Nakamura, E. *Heterocycles* **1996**, *42*, 565.

(w), 1887 (w), 1654 (s), 1600 (s), 1449 (s), 1328 (s), 1300 (s), 1223 (s) cm^{-1}; ^1H NMR: δ 7.59 (1H, d, *J* = 16 Hz), 7.55 (2H, m), 7.37 (3H, m), 7.28 (1H, d, *J* = 16 Hz), 6.82 (1H, q, *J* = 6.0 Hz), 1.89 (3H, d, *J* = 6.0 Hz), 1.88 (3H, s); ^{13}C NMR: δ 191.7, 142.5, 139.3, 137.4, 135.2, 129.9, 128.8, 128.1, 121.7, 14.80, 11.55. LRMS (ESI+) Calcd for $C_{13}H_{14}O$ $(M + Na)^+$: 209.1, Found $(M + Na)^+$: 209.1.



***trans*-1-Phenyl-5-methyl-1,4-hexadien-3-one (2.72).** Dialkylidene ketone **2.72** was prepared in 53% yield according to the procedure used to synthesize **2.67** on page 181. This compound has been previously reported.[9]

Synthesis of Ketone 2.122

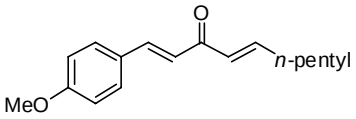


To 0.426 g (1.90 mmol) of (*E*)-1-iodoheptene in 2 mL of THF at –78 °C was added 0.76 mL (1.9 mmol) of a 2.5 M solution of *n*-BuLi in hexane dropwise over a 5 min period. This solution was allowed to stir at this temperature for 30 min and then transferred by canula to a solution of 0.215 g (0.951 mmol) of **2.187** in 10 mL of THF at –78 °C. After complete addition (5 min), TLC analysis showed complete consumption of the starting material after 15 min at –78 °C, so the reaction was subsequently quenched with saturated aqueous NH_4Cl. The unpurified mixture was transferred to a separatory

[9] Inaba, S. –I.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 1373.

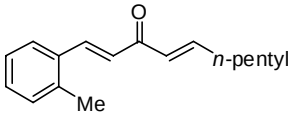
funnel with 1 M HCl and Et_2O. The organic layer was collected after shaking, and the aqueous layer was extracted with Et_2O (1x). The combined organics were washed with H_2O, then brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Silica gel chromatography (hexanes/EtOAc) of the mixture afforded 0.203 g (0.773 mmol, 81%) of (1*E*, 4*E*)-1-(3-chlorophenyl)deca-1,4-dien-3-one (**2.122**) as a light-yellow solid.

(1*E*,4*E*)-1-(3-Chlorophenyl)deca-1,4-dien-3-one, (2.122). Mp 38-40 ^oC. R_f = 0.19 (SiO_2, 15:1 Hexanes:EtOAc); IR (CH_2Cl_2 solution): 3031, (w), 2955 (s), 2924 (s), 2854 (s), 2817 (w), 1948 (w), 1665 (s), 1602 (s), 1463 (m), 1419 (m), 1293 (m), 1199 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.52 (1H, d, *J* = 16 Hz), 7.52 (1H, m), 7.39 (1H, dt, *J* = 6.8 Hz, *J* = 2.0 Hz), 7.25-7.34 (2H, m), 6.99 (1H, dd, *J* = 16 Hz, *J* = 7.2 Hz), 6.94 (1H, d, *J* = 16 Hz), 6.74 (1H, dt, *J* = 16 Hz, *J* = 1.6 Hz), 2.25 (2H, q, *J* = 7.2 Hz), 1.48 (2H, p, *J* = 7.2 Hz), 1.24-1.38 (4H, m) 0.871 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 188.7, 148.8, 141.0, 136.6, 134.8, 130.03, 130.00, 129.3, 127.7, 126.5, 125.7, 32.700, 31.38, 27.81, 22.44, 13.96. LRMS (APPI) Calcd for $C_{16}H_{19}ClO$ $(M + H)^+$: 263.1, Found $(M + H)^+$: 263.1.

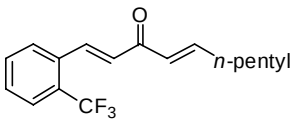


(1*E*,4*E*)-1-(4-Methoxyphenyl)deca-1,4-dien-3-one (2.123). Prepared in 90% yield according to the procedure used to synthesize **2.122** on page 182. An oil. R_f = 0.11 (SiO_2, 10:1 hexanes:EtOAc); IR (neat): 3006 (w), 2955 (m), 2930 (m), 2861 (m), 1659 (s), 1627 (s), 1590 (s), 1508 (s),

1420 (m), 1306 (m), 1256 (s), 1168 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.56 (1H, d, *J* = 16 Hz), 7.46 (2H, d, *J* = 8.8 Hz), 6.93 (1H, dt, *J* = 16 Hz, *J* = 7.2 Hz), 6.84 (2H, d, *J* = 8.8 Hz), 6.80 (1H, d, *J* = 16 Hz), 6.36 (1H, d, *J* = 16 Hz), 3.76 (3H, s), 2.20 (2H, q, *J* = 7.2 Hz), 1.44 (2H, p, *J* = 7.2 Hz), 1.20-1.36 (4H, m), 0.847 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 188.9, 161.3, 147.6, 142.5, 129.8, 129.1, 127.3, 122.5, 114.2, 55.17, 32.52, 31.27, 27.78, 22.34, 13.87. LRMS (APPI) Calcd for $C_{17}H_{22}O_2$ $(M + H)^+$: 259.2, Found $(M + H)^+$: 259.2.

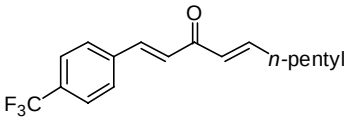


(1*E*,4*E*)-1-*o*-Tolyldeca-1,4-dien-3-one (2.124). Prepared in 89% yield according to the procedure used to synthesize **2.122** on page 182. An oil. R_f = 0.25 (SiO_2, 15:1 hexanes:EtOAc); IR (neat): 3025 (w), 2955 (s), 2930 (s), 2854 (m), 1658 (s), 1627 (s), 1596 (s), 1457 (m), 1319 (m), 1099 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.92 (1H, d, *J* = 16 Hz), 7.58 (1H, d, *J* = 7.6 Hz), 7.10-7.30 (3H, m), 6.99 (1H, dt, *J* = 16 Hz, *J* = 7.2 Hz), 6.89 (1H, d, *J* = 16 Hz), 6.39 (1H, dt, *J* = 16 Hz, *J* = 1.6 Hz), 2.41 (3H, s), 2.25 (2H, q, 7.2 Hz), 1.48 (2H, p, *J* = 7.6 Hz), 1.20-1.40 (4H, m), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 189.0, 148.2, 140.3, 137.9, 133.6, 130.6, 129.9, 129.5, 126.1, 125.5, 32.61, 31.31, 27.78, 22.38, 19.71, 13.90. LRMS (ESI+) Calcd for $C_{17}H_{22}O$ $(M)^+$: 242.2, Found $(M)^+$: 242.7.

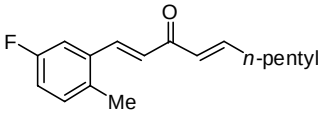


(1*E*,4*E*)-1-[2-(Trifluoromethyl)phenyl]deca-1,4-dien-3-one (2.125). Prepared in 79% yield according to the procedure used to synthesize **2.122** on page 182. A yellow oil. R_f = 0.22 (SiO_2, 16:1 hexanes:EtOAc);

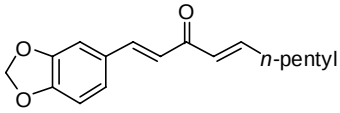
IR (neat): 2955 (s), 2930 (s), 2867 (m), 1659 (s), 1633 (s), 1602 (s), 1489 (m), 1313 (s), 1162 (s), 1124 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.93 (1H, d, *J* = 16 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.65 (1H, d, *J* = 8.0 Hz), 7.53 (1H, t, *J* = 8.0 Hz), 7.43 (1H, t, *J* = 8.0 Hz), 6.98 (1H, dt, *J* = 16 Hz, *J* = 7.2 Hz), 6.86 (1H, d, *J* = 16 Hz), 6.39 (1H, dt, *J* = 16 Hz, J = 1.6 Hz), 2.24 (2H, q, *J* = 6.8 Hz), 1.47 (2H, p, *J* = 7.2 Hz),1.22-1.36 (4H, m) 0.86 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 188.9, 149.2, 138.1, 133.8, 132.0, 129.4, 128.9, 128.85 (q, $^2J_{CF}$ = 30 Hz), 128.6, 127.7, 126.0 (q, $^3J_{CF}$ = 5.4 Hz), 123.9 (q, $^1J_{CF}$ = 272 Hz), 32.68, 31.31, 27.76, 22.39, 13.88. LRMS (ESI+) Calcd for $C_{17}H_{19}F_3O$ $(M)^+$: 296.1, Found $(M)^+$: 296.7.



(1*E*,4*E*)-1-[4-(Trifluoromethyl)phenyl]deca-1,4-dien-3-one (2.126). Prepared in 66% yield according to the procedure used to synthesize **2.122** on page 182. A yellow oil. R_f = 0.23 (SiO_2, 16:1 hexanes:EtOAc); IR (neat): 3043 (w), 2961 (s), 2930 (s), 2861 (m), 1923 (w), 1665 (s), 1633 (s), 1469 (m), 1419 (m), 1319 (s), 1167 (s), 1135 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.65 (1H, d, *J* = 8.7 Hz), 7.63 (1H, d, *J* = 8.7 Hz), 7.62 (1H, d, *J* = 16 Hz), 7.02 (1H, d, *J* = 16 Hz), 7.02 (1H, dt, *J* = 16 Hz, *J* = 6.6 Hz), 6.41 (1H, d, *J* = 16 Hz), 2.28 (2H, q, *J* = 6.6 Hz), 1.50 (2H, p, *J* = 7.5 Hz),1.24-1.40 (4H, m) 0.89 (3H, t, *J* =6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 188.7, 149.2, 140.8, 138.2, 131.6 (q, $^2J_{CF}$ = 32 Hz), 129.2, 128.3, 126.8, 125.8 (q, $^3J_{CF}$ = 3.1 Hz), 123.8 (q, $^1J_{CF}$ = 270 Hz), 32.76, 31.42, 27.85, 22.48, 13.93. LRMS (ESI+) Calcd for $C_{17}H_{19}F_3O$ $(M)^+$: 296.1, Found $(M)^+$: 296.7.

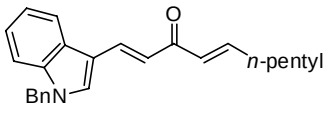


(1*E*,4*E*)-1-(5-Fluoro-2-methylphenyl)deca-1,4-dien-3-one (2.127). Prepared in 82% yield according to the procedure used to synthesize **2.122** on page 182. A yellow oil. R_f = 0.11 (SiO_2, 20:1 hexanes:EtOAc); IR (neat): 2955 (m), 2930 (s), 2861 (m), 1659 (s), 1627 (s), 1489 (s), 1338 (m), 1237 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.83 (1H, dd, *J* = 16 Hz, *J* = 1.6 Hz), 7.26 (1H, dd, *J* = 9.6 Hz, *J* = 2.4 Hz), 7.12 (1H, dd, *J* = 8.4 Hz, *J* = 5.6 Hz), 6.99 (1H, dt, *J* = 16 Hz, *J* = 6.8 Hz), 6.95 (1H, dt, *J* = 8.4 Hz, *J* = 2.4 Hz), 6.86 (1H, d, *J* = 16 Hz), 6.36 (1H, dt, *J* = 16 Hz, *J* = 1.6 Hz), 2.37 (3H, s), 2.26 (2H, q, *J* = 6.8 Hz), 1.49 (2H, p, *J* = 7.2 Hz), 1.21-1.37 (4H, m), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 188.8, 161.2 (d, $^1J_{CF}$ = 242 Hz), 148.8, 139.2, 135.4 (d, $^3J_{CF}$ = 7.8 Hz), 133.6, 132.0 (d, $^3J_{CF}$ = 7.8 Hz), 129.6, 126.3, 116.7 (d, $^2J_{CF}$ = 21 Hz), 112.4 (d, $^2J_{CF}$ = 22 Hz), 32.72, 31.38, 27.83, 22.45, 19.03, 13.96; ^{19}F NMR ($CDCl_3$): δ 93.28 (m). LRMS (APPI) Calcd for $C_{17}H_{21}FO$ (M + H)$^+$: 261.2, Found (M + H)$^+$: 261.2.

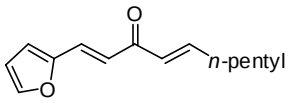


(1*E*,4*E*)-1-(Benzo[*d*][1,3]dioxol-5-yl)deca-1,4-dien-3-one (2.128). Prepared in 87% yield according to the procedure used to synthesize **2.122** on page 182. An off-white solid. Mp = 40-44 °C. R_f = 0.23 (SiO_2, 9:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 2961 (s), 2930 (s), 2861 (s), 1658 (s), 1626 (s), 1589 (s), 1488 (s), 1444 (s), 1362 (m), 1255 (s), 1205 (m), 1098 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.51 (1H, d, *J* = 16 Hz), 7.04 (1H, s,), 7.01 (1H, d, *J* = 8.4 Hz), 6.94 (1H, dt, *J* = 16 Hz, *J* = 7.2 Hz), 6.77 (1H, d, *J* = 16 Hz), 6.77 (1H, d, *J* = 8.4 Hz), 6.36 (1H, dt, J = 16 Hz, J = 1.6 Hz), 5.96 (2H, s), 2.22 (2H, q, *J* = 7.2 Hz), 1.46 (2H, p, *J* = 7.2

Hz), 1.20-1.37 (4H, m) 0.86 (3H, t, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$): δ 188.9, 149.6, 148.2, 147.9, 142.6, 129.25, 129.16, 124.8, 122.8, 108.5, 106.4, 101.5, 32.61, 31.35, 27.84, 22.41, 13.94. LRMS (APPI) Calcd for $C_{17}H_{20}O_3$ $(M + H)^+$: 273.1, Found $(M + H)^+$: 273.1.

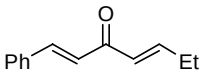


(1*E*,4*E*)-1-(1-benzyl-1*H*-indol-3-yl)deca-1,4-dien-3-one (2.129). Prepared in 88% yield according to the procedure used to synthesize **2.122** on page 182. A yellow solid. Mp 84-88 °C. R_f = 0.21 (SiO_2, 5:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3106 (m), 3037 (w), 2961 (m), 2930 (m), 2854 (m), 1658 (m), 1627 (s), 1576 (s), 1526 (s), 1463 (m), 1387 (s), 1350 (m), 1281 (m), 1173 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.94-8.00 (1H, m), 7.91 (1H, d, J = 16 Hz), 7.44 (1H, s), 7.16-7.26 (6H, m), 7.13 (2H, dd, J = 7.6 Hz, J = 2 Hz), 6.99 (1H, dt, J = 16 Hz, J = 8.0 Hz), 6.99 (1H, d, J = 16 Hz), 6.44 (1H, dt, J = 16 Hz, J = 1.6 Hz), 5.30 (2H, s), 2.26 (2H, q, J = 8.0 Hz), 1.51 (2H, p, J = 7.2 Hz) 1.23-1.41 (4H, m), 0.90 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 189.2, 146.7, 137.7, 136.5, 136.0, 133.1, 133.0, 129.5, 128.9, 128.0, 126.9, 126.3, 123.1, 121.5, 120.7, 113.2, 110.5, 50.46, 32.65, 31.44, 27.98, 22.49, 14.01. LRMS (APPI) Calcd for $C_{25}H_{27}NO$ $(M + H)^+$: 358.2, Found $(M + H)^+$: 358.2.



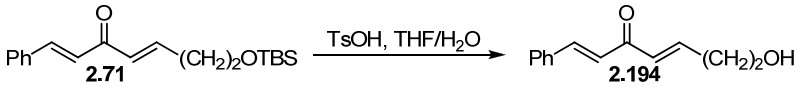
(1*E*,4*E*)-1-(Furan-2-yl)deca-1,4-dien-3-one (2.130). Prepared in 86% yield according to the procedure used to synthesize **2.122** on page 182. A yellow oil. R_f = 0.15 (SiO_2, 15:1 hexanes:EtOAc); IR (neat): 3124 (w), 3037 (w), 2955 (s), 2930 (s), 2861 (m), 1658 (s), 1633 (s), 1595 (s), 1482 (m), 1306 (m),

1217 (m), 1098 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.44 (1H, s), 7.36 (1H, d, *J* = 16 Hz), 6.93 (1H, dt, *J* = 16 Hz, *J* = 6.8 Hz), 6.85 (1H, d, *J* = 16 Hz), 6.60 (1H, d, *J* = 3.2 Hz), 6.42 (1H, m), 6.29 (1H, d, *J* = 16 Hz), 2.20 (2H, q, *J* = 6.8 Hz), 1.44 (2H, p, *J* = 6.8 Hz),1.17-1.36 (4H, m), 0.85 (3H, t, *J* =6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 188.6, 151.4, 148.0, 144.6, 129.7,128.9, 121.8, 115.4, 112.4, 32.60, 31.31, 27.79, 22.39, 13.90. LRMS (APPI) Calcd for $C_{14}H_{18}O_2$ $(M + H)^+$: 219.1, Found $(M + H)^+$: 219.1.



(1*E*,4*E*)-1-Phenylhepta-1,4-dien-3-one (2.193). Prepared in 90% yield according to the procedure used to synthesize **2.62** on page 178. A yellow oil. R_f = 0.29 (SiO_2, 10:1 hexanes:EtOAc); IR (neat): 3031 (w), 2968 (m), 2936 (m), 2879 (w), 1659 (s), 1633 (s), 1602 (s), 1450 (m), 1349 (m), 1199 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.63 (1H, d, *J* = 16 Hz), 7.56 (2H, m), 7.38 (3H, m), 7.05 (1H, dt, *J* = 16 Hz, *J* = 6.4 Hz), 6.97 (1H, d, *J* = 16 Hz), 6.42 (1H, d, *J* = 16 Hz), 2.30 (2H, p, *J* = 7.2 Hz), 1.11 (3H, t, *J* = 7.2 Hz) 1.10-1.40 (5H, m); ^{13}C NMR ($CDCl_3$): δ 189.4, 149.7, 143.0, 134.7, 130.2, 128.8, 128.23, 128.19, 124.6, 25.77, 12.30. LRMS (APPI) Calcd for $C_{13}H_{14}O$ $(M + H)^+$: 187.1, Found $(M + H)^+$: 187.1.

Synthesis of 2.194

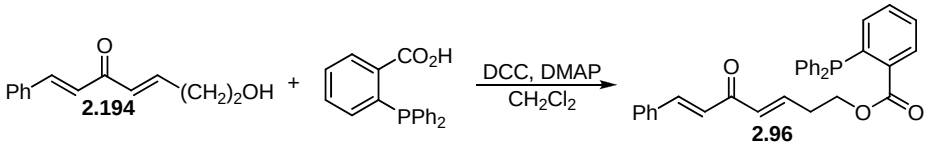


To a solution of 0.763 g (2.41 mmol) of **2.71** in 12 mL of 3:1 THF:H_2O was added 0.458 g (2.41 mmol) of *p*-toluenesulfonic acid monohydrate under a N_2

atmosphere. This mixture was allowed to stir at room temperature and monitored by TLC. The starting material was consumed after 1h as evident by TLC analysis, and H_2O was then added, followed by extraction with Et_2O. The combined organics were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Silica gel chromatography (hexanes/EtOAc) of the mixture afforded 0.479 g (2.37 mmol, 98%) of **2.194** as a yellow oil.

(1*E*,4*E*)-7-Hydroxy-1-phenylhepta-1,4-dien-3-one (2.194). R_f = 0.30 (SiO_2, 1:2 hexanes:EtOAc); IR (neat): 3415 (s, br), 3058 (w), 2939 (m), 2878 (m), 1958 (w), 1659 (s), 1628 (s), 1598 (s), 1494 (m), 1449 (m), 1333 (s), 1308 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.61 (1H, d, *J* = 16 Hz), 7.48-7.54 (2H, m), 7.31-7.37 (3H, m), 6.98 (1H, dt, *J* = 16 Hz, *J* = 7.0 Hz), 6.93 (1H, d, *J* = 16 Hz), 6.50 (1H, dt, *J* = 16 Hz, *J* = 1.6 Hz), 3.78 (2H, t, *J* = 6.2 Hz), 2.62-2.92 (1H, br s), 2.51 (2H, dq, *J* = 7.0 Hz, *J* = 1.6 Hz); ^{13}C NMR ($CDCl_3$): δ 189.1, 144.4, 143.4, 134.5, 130.9, 130.4, 128.8, 128.2, 124.5, 60.84, 35.87. LRMS (ESI+) Calcd for $C_{13}H_{14}O_2$ $(M + H)^+$: 203.1, Found $(M + H)^+$: 203.1.

Synthesis of 2.96

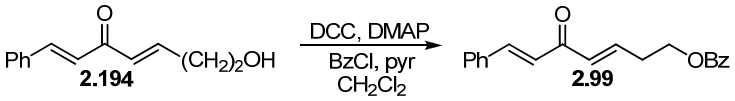


To 0.200 g (0.968 mmol) of **2.194** in 1.9 mL of CH_2Cl_2 was added 0.386 g (1.26 mmol) of *o*-diphenylphosphinobenzoic acid, 0.260 g (1.26 mmol) of N,N'-dicyclohexylcarbodiimide (DCC), and 11.9 mg (0.0968 mmol) of 4-

(dimethylamino)pyridine (DMAP) sequentially under N_2. This mixture was then allowed to stir at ambient temperature for 2h, and the mixture was subsequently filtered through celite using CH_2Cl_2. Volatile material was removed under reduced pressure, and the resultant oil purified by silica gel chromatography (hexanes/EtOAc) to afford 0.348 g (0.709 mmol, 73%) of **2.96** as a light-yellow solid.

(3*E*,6*E*)-5-Oxo-7-phenylhepta-3,6-dienyl 2-(diphenylphosphino)benzoate (2.96). Mp 140-145 ^{o}C. R_f = 0.20 (SiO_2, 4:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3411 (br, m), 3058 (m), 2957 (m), 1967 (w), 1891 (w), 1717 (s), 1662 (s), 1628 (s), 1601 (s), 1433 (s), 1339 (m), 1275 (s), 1189 (s), 1122 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.00-8.07 (1H, m), 7.63 (1H, d, *J* = 16 Hz), 7.51-7.59 (2H, m), 7.20-7.42 (16H, m), 6.96 (1H, d, *J* = 16 Hz), 6.89 (1H, dt, *J* = 16 Hz, *J* = 6.8 Hz), 6.46 (1H, d, *J* = 16 Hz), 4.32 (2H, t, *J* = 6.4 Hz), 2.55 (2H, q, *J* = 6.4 Hz); ^{1}H NMR (C_6D_6): δ 8.04-8.10 (1H, m), 7.70 (1H, d, *J* = 16 Hz), 7.32-7.46 (4H, m), 6.85-7.25 (14H, m), 6.81 (1H, d, *J* = 16 Hz), 6.73 (1H, dt, *J* = 16 Hz, *J* = 6.8 Hz), 6.16 (1H, d, *J* = 16 Hz), 3.94 (2H, t, *J* = 6.4 Hz), 2.00 (2H, q, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$): δ 188.7, 166.6, 143.3, 142.6, 140.3, 140.1, 137.8, 137.7, 134.7, 134.3, 133.9, 133.7, 132.0, 131.0, 130.6, 130.4, 128.8, 128.6, 128.5, 128.4, 128.3, 124.7, 63.11, 31.74. ^{13}C NMR (C_6D_6): δ 187.9, 167.0, 143.1, 142.5, 139.3, 139.2, 138.8, 135.2, 134.8, 134.6, 132.4, 131.9, 131.3, 130.5, 129.3, 129.1, 128.9, 128.8, 125.8, 63.67, 32.22. ^{31}P NMR (C_6D_6): δ -2.86. LRMS (ESI+) Calcd for $C_{32}H_{27}O_3P$ $(M + H)^+$: 491.2, Found $(M + H)^+$: 491.1.

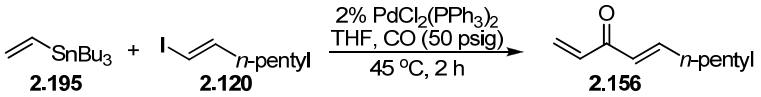
Synthesis of 2.99



To a solution of 96.7 mg (0.478 mmol) of **2.194** in 1.9 mL of CH_2Cl_2 at 0 ^oC was added 0.10 mL of pyridine, 12 mg of DMAP, and 0.14 mL of benzoyl chloride, sequentially. Reaction progress was monitored by TLC, and after 1h at 0 ^oC, 0.05 mL of pyridine and 0.07 mL of benzoyl chloride were added. After an additional 30 min at 0^oC, starting material had been consumed as evident by TLC analysis. Saturated aqueous $NaHCO_3$ was added, and the aqueous layer extracted with Et_2O (1x). The organic layer was washed with 1M HCl (2x) and dried with anhydrous Na_2SO_4. After removal of volatile material under reduced pressure, the mixture was purified by silica gel chromatography (hexanes/EtOAc) to afford 124 mg (0.405 mmol, 85%) of **2.99** as an off-white solid.

(3*E*,6*E*)-5-Oxo-7-phenylhepta-3,6-dienyl benzoate (2.99). Mp 60-66 ^oC. R_f = 0.13 (SiO_2, 6:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3054 (m), 3025 (m), 2919 (m), 2848 (m), 1720 (s), 1661 (s), 1602 (s), 1450 (m), 1273 (s), 1188 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.96-8.06 (1H, m), 7.63 (1H, d, *J* = 16 Hz), 7.49-7.59 (3H, m), 7.33-7.47 (5H, m), 7.02 (1H, dt, *J* = 16 Hz, *J* = 6.8 Hz), 6.94 (1H, d, *J* = 16 Hz), 6.57 (1H, d, *J* = 16 Hz), 4.48 (2H, t, *J* = 6.4 Hz), 2.75 (2H, q, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$): δ 188.7, 166.3, 143.5, 142.6, 134.6, 133.0, 131.0, 130.4, 129.9, 129.5, 128.9, 128.35, 128.26, 124.8, 62.84, 32.03. LRMS (ES+) Calcd for $C_{20}H_{18}O_3$ $(M + H)^+$: 307.1, Found $(M + H)^+$: 307.1.

Synthesis of 2.156

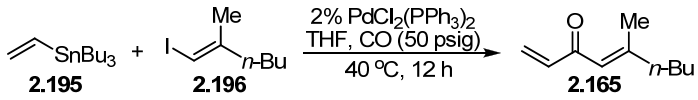


A pressure tube with a magnetic stir-bar was charged with 62.7 mg (0.0892 mmol) of *trans*-bis(triphenylphosphino)palladium dichloride, 4.5 mL of anhydrous THF, 1.00 g (4.46 mmol) of colorless (*E*)-1-iodoheptene (**2.120**), and 1.57 mL (1.70 g, 5.35 mmol) of tri-*n*-butyl(vinyl)tin (**2.195**). The tube was then charged with 50 psig of carbon monoxide gas, and after stirring for 1 min, the pressure was released. This was repeated two more times, and the tube was subsequently charged with 50 psig of CO and immersed in an oil bath at 40 ^{o}C and heated overnight. After cooling the reaction to room temperature, the reaction was vented and concentrated under reduced pressure. The residue was filtered through neutral alumina using 100 mL of 9:1 hexanes:EtOAc and then concentrated under reduced pressure. To this mixture was added 65 mL of Et_2O followed by 65 mL of 50% saturated aqueous KF, and the resultant biphasic mixture was allowed to stir rapidly for 2 h. This mixture was then filtered through celite, and the organic layer was collected, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the material using silica gel chromatography (hexanes/EtOAc) afforded 462 mg (3.03 mmol, 68%) of **2.156**.

(*E*)-Deca-1,4-dien-3-one (2.156). A yellow oil. R_f = 0.23 (SiO_2, 25:1 hexanes:EtOAc); IR (neat): 3021 (w), 2962 (s), 2932 (s), 2865 (s), 1662 (s), 1632 (s), 1611 (s), 1468 (m), 1396 (s), 1341 (w), 1282 (w), 1105 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.88 (1H, dt, J = 16

Hz, J = 6.8 Hz), 6.55 (1H, dd, J = 17 Hz, J = 10 Hz), 6.29 (1H, dt, J = 16 Hz, J = 1.6 Hz), 6.21 (1H, dd, J = 17 Hz, J = 1.6 Hz), 5.74 (1H, dd, J = 10 Hz, J = 1.6 Hz), 2.18 (2H, q, J = 7.2 Hz), 1.42 (2H, p, J = 7.2 Hz), 1.18-1.34 (4H, m), 0.83 (3H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 189.5, 148.9, 134.8, 128.04, 127.98, 32.58, 31.29, 27.73, 22.36, 13.87. LRMS (ESI+) Calcd for $C_{10}H_{16}O$ $(M + H)^+$: 153.1, Found $(M + H)^+$: 153.1.

Synthesis of 2.165



2.195 **2.196** **2.165**

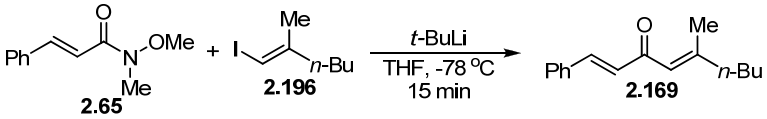
A pressure tube with a magnetic stir-bar was charged with 70.2 mg (0.100 mmol) of *trans*-bis(triphenylphosphino)palladium dichloride, 5.0 mL of anhydrous THF, 1.12 g (5.00 mmol) of colorless **2.196**,[10] and 1.75 mL (1.90 g, 6.00 mmol) of tri-*n*-butyl(vinyl)tin (**2.195**). The tube was then charged with 50 psig of carbon monoxide gas, and after stirring for 1 min, the pressure was released. This was repeated two more times, and the tube was subsequently charged with 50 psig of CO and immersed in an oil bath at 50 °C. After ~1 h the pressure had dropped to 30 psig, and the system was repressurized to 50 psig. After an additional 2 h at 50 °C, the pressure again had dropped to 30 psig, so the system was repressurized to 45 psig and heated for an additional 2 h. The reaction was then cooled to room temperature, vented, and concentrated under reduced pressure. The residue was filtered through neutral alumina using 100 mL of 9:1 hexanes:EtOAc and concentrated under reduced pressure. To this mixture was added 100 mL of Et_2O

[10] (a) Morill, C.; Beutner, G. L.; Grubbs, R. H. *J. Org. Chem.* **2006**, *71*, 7813. (b) Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639.

followed by 100 mL of 50% saturated aqueous KF, and the resultant biphasic mixture was allowed to stir rapidly for 2 h. This mixture was then filtered through celite, and the organic layer was collected, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the material using silica gel chromatography (hexanes/EtOAc) afforded 493 mg (3.24 mmol, 65%) of **2.163**.

(*E*)-5-Methylnona-1,4-dien-3-one (2.163). A yellow oil. R_f = 0.18 (SiO_2, 30:1 hexanes:EtOAc); IR (neat): 3095 (w), 3018 (w), 2954 (s), 2930 (s), 2872 (m), 2860 (m), 1677 (s), 1662 (s), 1625 (s), 1598 (s), 1458 (m), 1400 (s), 1232 (m), 1132 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.38 (1H, dd, *J* = 18 Hz, *J* = 11 Hz), 6.23 (1H, s), 6.18 (1H, dd, *J* = 18 Hz, *J* = 1.2 Hz), 5.71 (1H, dd, *J* = 11 Hz, *J* = 1.2 Hz), 2.15 (2H, t, *J* = 7.6 Hz), 2.13 (3H, s), 1.45 (2H, p, *J* = 7.6 Hz), 1.30 (2H, h, *J* = 7.6 Hz), 0.89 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$): δ 190.4, 160.9, 138.3, 126.8, 121.3, 41.18, 29.72, 22.39, 19.65, 13.90. LRMS (ESI+) Calcd for $C_{10}H_{16}O$ $(M + H)^+$: 153.1, Found $(M + H)^+$: 153.1.

Synthesis of 2.169



To 0.383 g (1.71 mmol) of **2.196** in 1.8 mL of THF at –78 °C was added 2.6 mL (3.4 mmol) of a 1.3 M solution of *t*-BuLi in pentane dropwise over 5 min. This solution was allowed to stir at this temperature for 30 min and then transferred by canula to a solution of 0.273 g (1.43 mmol) of **2.65** (dried by azeotropic removal of water with

benzene) in 14 mL of THF at –78 ^{o}C. After complete addition (10 min), the reaction was allowed to stir for 15 min at –78 ^{o}C. To the reaction was then added 0.75 mL of MeOH, the dry-ice acetone bath was removed, and water was added. After reaching room temperature, the mixture was transferred to a separatory funnel with water and Et_2O. The organic layer was collected after shaking, and the aqueous layer was extracted with Et_2O (1x). The combined organics were sequentially washed with saturated aqueous $NaHCO_3$, saturated aqueous $Na_2S_2O_3$, and again with saturated aqueous $NaHCO_3$. The organic layer was finally dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Silica gel chromatography (1% TEA in hexanes/EtOAc) of the mixture afforded 0.232 g (1.02 mmol, 71%) of **2.169** as a yellow oil.

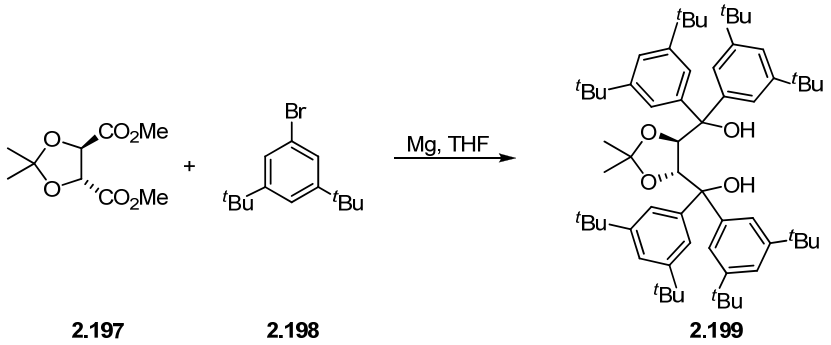
(1*E*,4*E*)-5-Methyl-1-phenylnona-1,4-dien-3-one (2.169). R_f = 0.23 (SiO_2, 1% TEA in 19:1 Hexanes:EtOAc); IR (neat): 3028 (w), 2957 (m), 2930 (m), 2872 (m), 1674 (s), 1650 (s), 1622 (s), 1576 (m), 1494 (m), 1451 (m), 1385 (w), 1327 (m), 1332 (m), 1202 (m), 1168 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.55 (1H, d, *J* = 16 Hz), 7.49-7.56 (2H, m), 7.31-7.40 (3H, m), 6.78 (1H, d, *J* = 16 Hz), 6.30 (1H, q, *J* = 1.2 Hz), 2.14-2.24 (5H, m), 1.44-1.54 (2H, m), 1.34 (2H, h, *J* = 7.6 Hz), 0.92 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$): δ 190.1, 160.2, 141.7, 134.9, 130.0, 128.8, 128.3, 128.1, 122.9, 41.17, 29.77, 22.41, 19.66, 13.94. LRMS (ESI+) Calcd for $C_{16}H_{20}O$ $(M + H)^+$: 229.2, Found $(M + H)^+$: 229.1.

3. Chiral Ligand Syntheses

TADDOL syntheses:

The requisite TADDOLs were prepared via Grignard addition to the acetonide protected methyl ester of enantiomerically pure tartaric acid using the known route.[47] An example is given below for the preparation of 3,5-di-*t*-butylphenylTADDOL (**2.199**).

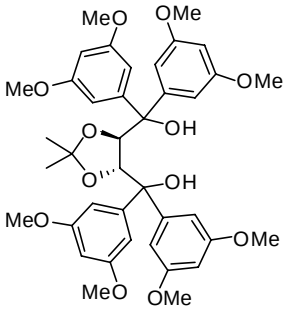
Synthesis of Diol 2.199



2.197 **2.198** **2.199**

To a flame-dried 100 mL 2-neck round-bottom flask with magnetic stir-bar and a reflux condenser was added 0.487 g (20.3 mmol) of freshly cracked Mg turnings. The Mg was then flame dried followed by the addition of 1 crystal of I_2. An addition funnel was fitted, and 5.02 g (18.6 mmol) of **2.198** in 19 mL of THF was added dropwise. After complete addition, the reaction had reached reflux, and an oil bath was applied to keep the reaction at a gentle reflux for 2 h. The resultant mixture was cooled to 0 ^{o}C, and 0.737 g (3.38 mmol) of **2.197** in 6 mL of THF was added. After complete addition (5 min), the mixture was heated to reflux overnight, and subsequently, quenched at 0 ^{o}C by the addition of 15 mL of saturated aqueous NH_4Cl, followed by addition of 15 mL of water. This mixture was then allowed to stir at room temperature for ~1 h or until all the

excess Mg metal had been consumed. The mixture was transferred to a separatory funnel and extracted with EtOAc (3x). The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. Silica gel chromatography of the mixture afforded 2.65 g (2.89 mmol, 86%) of **2.199** as an off-white solid.

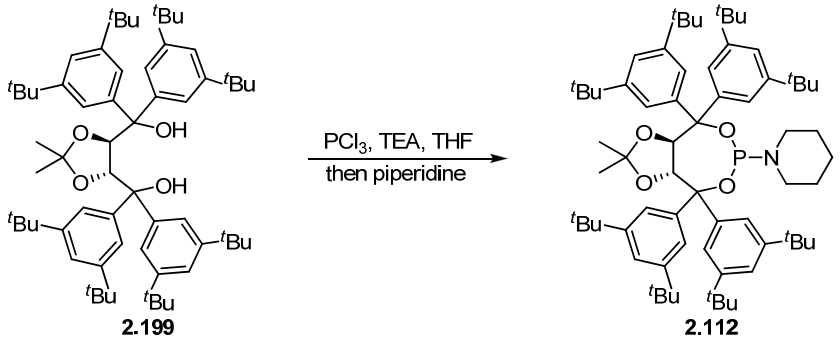


[(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl]bis[bis(3,5-dimethoxyphenyl)methanol] (2.200). Prepared in 78% yield according to the procedure used to synthesize **2.199** on page 196. Note that 7.0 equiv of 1-bromo-3,5-dimethoxybenzene and 7.0 equiv of Mg metal was used. A white solid. R_f = 0.11 (SiO_2, 2:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3329 (s, br), 2991 (s), 2940 (s), 2835 (s), 1599 (s), 1459 (s), 1421 (s), 1375 (m), 1345 (s), 1307 (s), 1202 (s), 1160 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.73 (4H, s), 6.50 (4H, s), 6.35 (2H, s), 6.26 (2H, s), 4.50 (2H, s), 4.49 (2H, s), 3.70 (12H, s), 3.63 (12H, s), 1.15 (6H, s); ^{13}C NMR ($CDCl_3$): δ 160.1, 159.7, 147.4, 144.8, 109.0, 106.7, 106.0, 99.30, 99.00, 81.46, 77.97, 55.22, 55.09, 27.28. LRMS (ESI+) Calcd for $C_{39}H_{46}O_{12}$ $(M - 2H_2O + H)^+$: 671.3, Found $(M - 2H_2O + H)^+$: 671.3.

Phosphoramidite ligand syntheses:

Phosphoramidites were prepared by reaction of PCl_3 with the appropriate TADDOL and amine in the presence of TEA. An example is given below for **2.112**. **2.107**,[48,11] **2.108**,[12] **2.109**,[48a,73] **2.110**,[13] and **2.112**[14] have been prepared previously.

Synthesis of 2.112

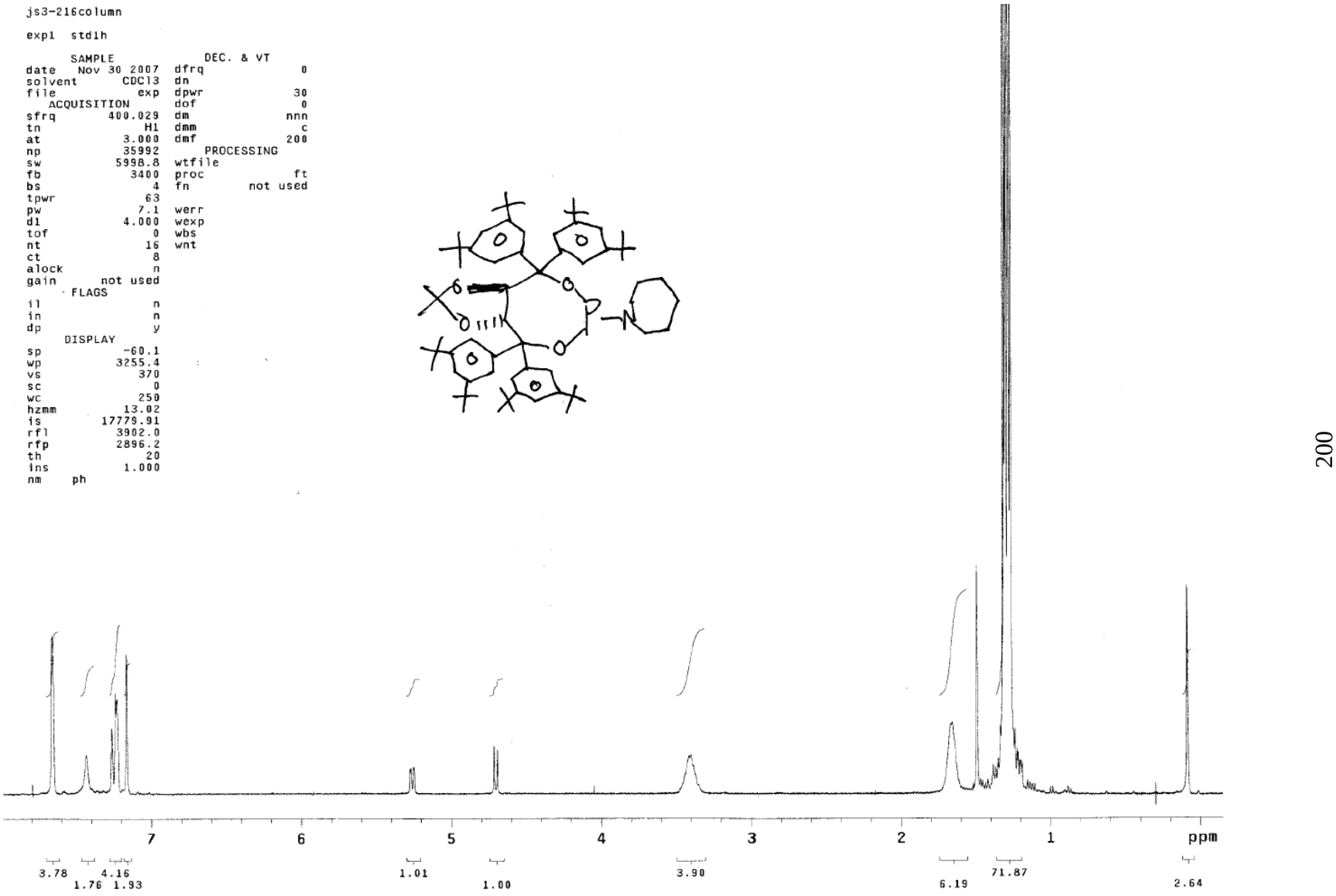


To 0.179 g (0.195 mmol) of **2.199** in an oven-dried 2-dram vial with stir-bar, under N_2, was added 0.80 mL of THF. The mixture was cooled to 0 ^oC, and 0.092 mL (0.66 mmol) of TEA was added, followed by dropwise addition of 18.7 μL (0.215 mmol) of PCl_3. A white precipitate immediately formed, and the reaction was warmed to room temperature and allowed to stir for 1 h. After cooling to 0 ^oC, 0.14 mL (1.4 mmol) of piperidine was added, and the reaction was allowed to warm to room temperature and allowed to stir for 3 h. The reaction was then diluted with Et_2O and filtered through a pad of celite. Removal of volatile material under reduced pressure, followed by

[11] Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; Huevel, A. V. D.; Levêque, J. M.; Mazé, M.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011.
[12] Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370.
[13] Boele, M. D. K.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; de Vries, J. G.; van Leeuwen, P. W. M. N.; van Strijdonck, G. P. F. *Chem. Eur. J.* **2004**, *10*, 6232.
[14] Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5505.

purification using silica gel chromatography (hexanes/EtOAc) afforded 0.163 g (0.158 mmol, 81%) of **2.112** as a white foamy solid.

[3,5-(^{t}Bu)$_2$TADDOL]PNC$_5$H$_{10}$ (2.112). Mp 192-200 ^{o}C (sealed capillary). R_f = 0.33 (SiO_2, 30:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3075 (w), 2966 (s), 2906 (m), 2865 (m), 1784 (w), 1599 (m), 1450 (m), 1358 (m), 1252 (m), 1201 (m), 1164 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.66 (4H, s), 7.44 (2H, br s), 7.27 (1H, s), 7.21-7.25 (3H, m), 7.17 (2H, s), 5.26 (1H, dd, *J* = 6.8 Hz, *J* = 1.6 Hz), 4.70 (1H, d, *J* = 6.8 Hz), 3.32-3.49 (4H, m), 1.60-1.75 (6H, m), 1.46 (3H, s), 1.31 (18H, s), 1.30 (18H, s), 1.28 (18H, s), 1.27 (18H, s), 0.09 (3H, s); ^{13}C NMR ($CDCl_3$): δ 149.5, 149.1, 148.7, 148.6, 146.5, 146.19, 146.17, 142.1, 141.2, 123.7, 122.0, 121.6, 120.5, 120.1, 120.0, 119.8, 109.7, 83.79, 83.62, 82.43, 82.35, 81.06, 45.10 (d, $^2J_{CP}$ = 20 Hz), 35.01, 34.94, 34.83, 31.56, 31.52, 28.02, 27.53 (d, $^3J_{CP}$ = 4.7 Hz), 25.50, 24.04. ^{31}P NMR ($CDCl_3$): δ 137.8. LRMS (ESI+) Calcd for $C_{68}H_{102}NO_4P$ $(M)^+$: 1027.8, Found $(M)^+$: 1027.8. $[\alpha]_D^{20}$ = -40^o (*c* = 3.0, $CHCl_3$).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pw 7.1
d1 4.000
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ct 8
alock n
gain not used
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in n
dp y
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dof 0
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dmm c
dmf 200
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werr
wexp
wbs
wnt
7
6
5
4
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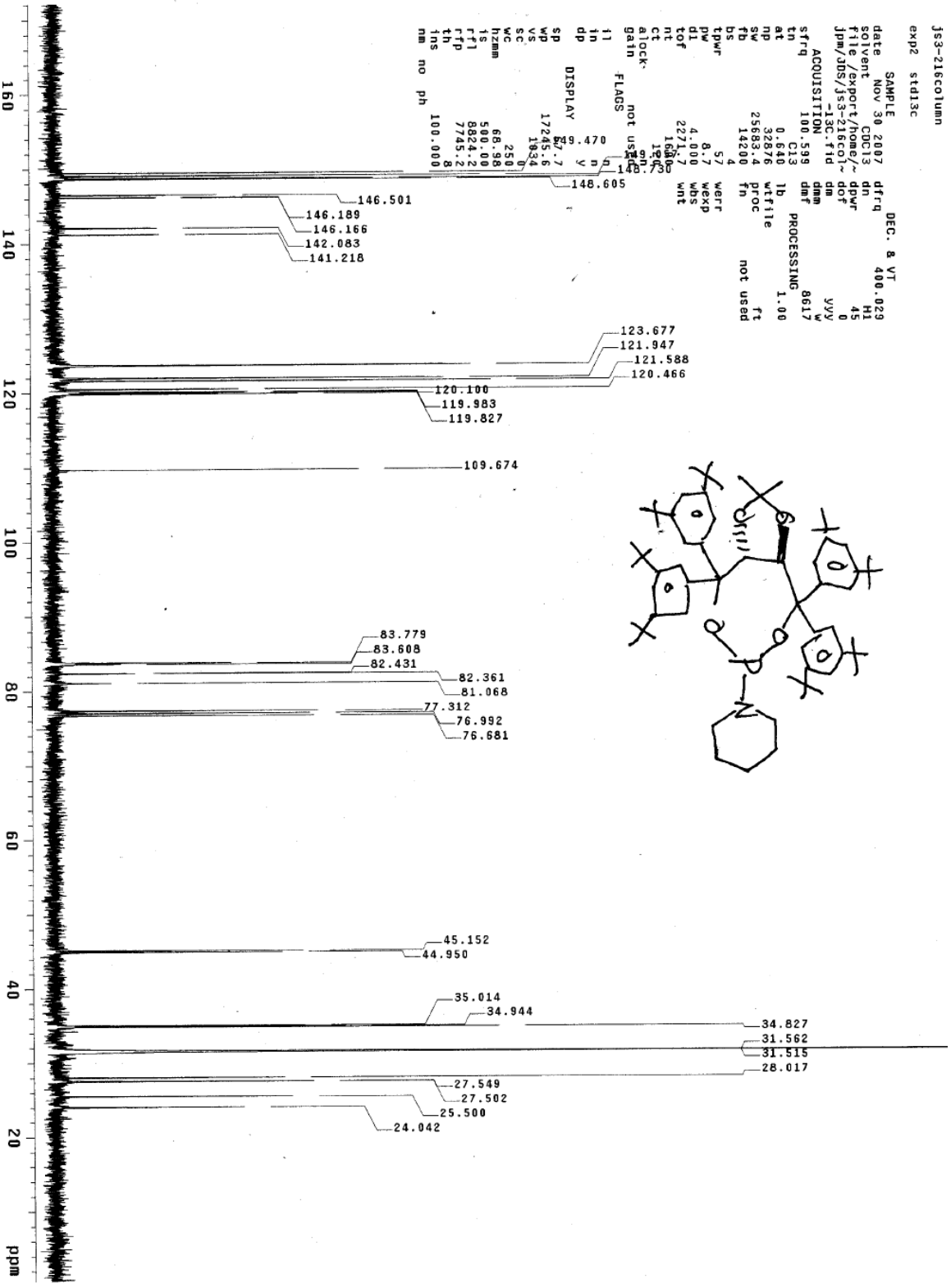
6.19
71.87
2.64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date Nov 30 2007
solvent CDCl3
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sw 25683.4
fb 14200
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tpwr 57
pw 8.7
dl 4.000
tof 2271.7
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ct 1680
alock n
gain n
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vs 1834
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is 500.00
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dmm w
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wrr
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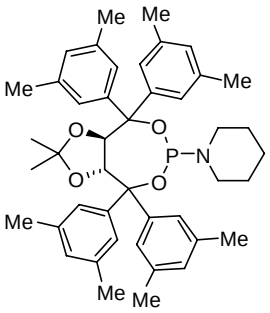
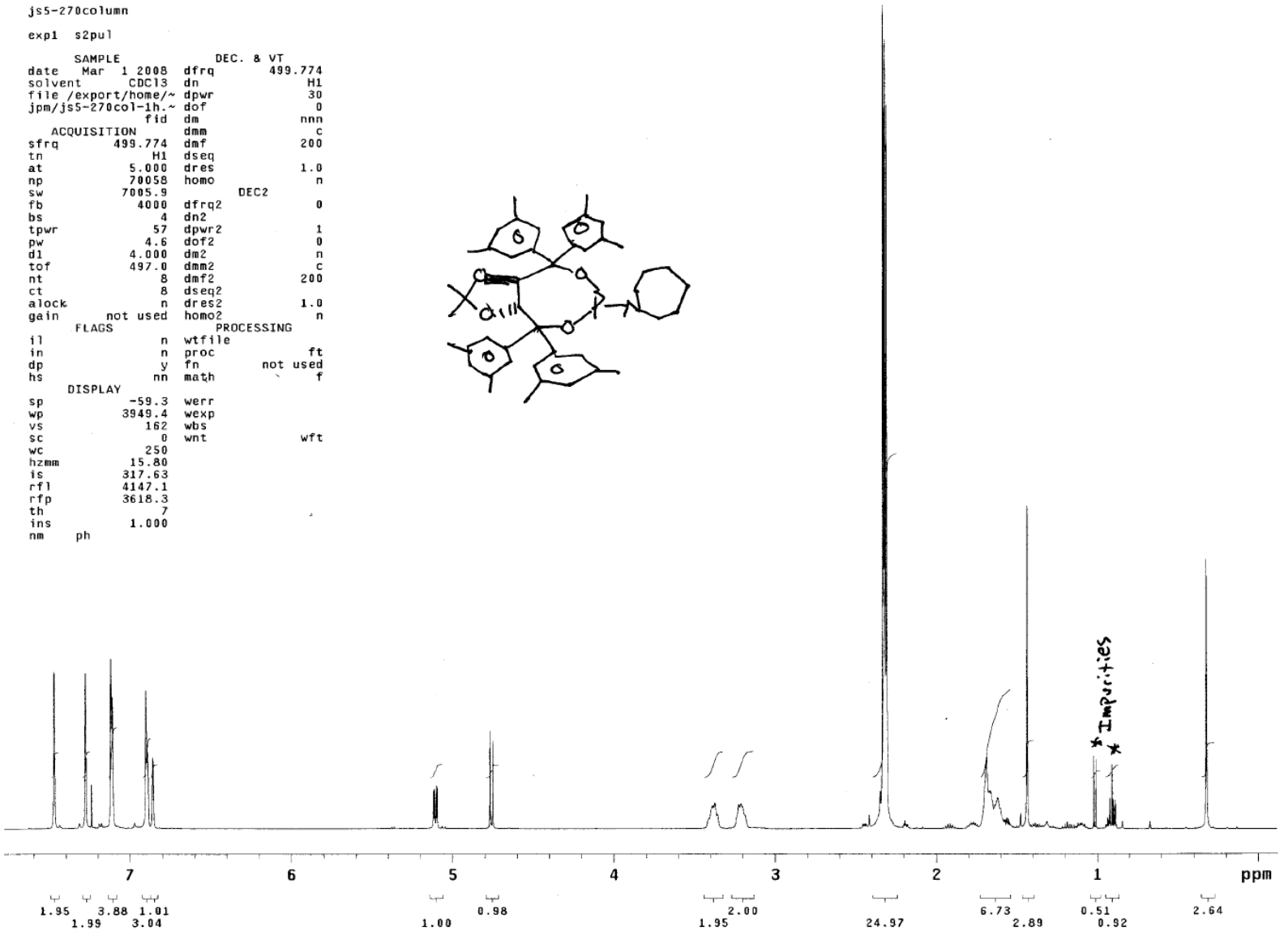


[3,5-xylylTADDOL]PNC$_5$H$_{10}$ (2.159). Prepared in 75% yield according to the procedure used to synthesize **2.112** on page 198. A white solid. R_f = 0.15 (SiO_2, 30:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3050 (m), 2991 (s), 2928 (s), 2845 (s), 1755 (w), 1607 (s), 1442 (s), 1379 (s), 1332 (m), 1253 (s), 1219 (s), 1160 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.47 (2H, s), 7.28 (2H, s), 7.12 (2H, s), 7.11 (2H, s), 6.90 (2H, s), 6.89 (1H, s), 6.86 (1H, s), 5.11 (1H, dd, *J* = 8.5 Hz, *J* = 3.5 Hz), 4.76 (1H, d, *J* = 8.5 Hz), 3.32-3.45 (2H, m), 3.14-3.25 (2H, m), 2.330 (6H, s), 2.323 (6H, s), 2.316 (6H, s), 2.307 (6H, s), 1.55-1.75 (6H, m), 1.44 (3H, s), 0.322 (3H, s); ^{13}C NMR ($CDCl_3$): δ 147.2, 146.77, 146.75, 141.95, 141.94, 141.91, 137.0, 136.6, 136.4, 136.1, 128.9, 128.7, 128.6, 128.5, 126.9, 126.6, 126.5, 125.0, 111.3, 83.09, 83.06, 82.71, 82.54, 81.21, 81.07, 81.01, 44.98 (d, $^2J_{CP}$ = 20 Hz), 34.65, 27.69, 27.00 (d, $^3J_{CP}$ = 3.6 Hz), 25.45, 25.26, 21.66, 21.59, 21.54. ^{31}P NMR ($CDCl_3$): δ 138.2. LRMS (ESI+) Calcd for $C_{44}H_{54}NO_4P$ $(M + H)^+$: 692.4, Found $(M + H)^+$: 692.4. $[\alpha]_D^{20}$ = -113° (*c* = 2.3, $CHCl_3$).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SAMPLE
date Mar 1 2008
solvent CDCl3
file /export/home/~
jpm/js5-270col-1h.~
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sw 7005.9
fb 4000
bs 4
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pw 4.6
d1 4.000
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ct 8
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in n
dp y
hs nn
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is 317.63
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dfrq 499.774
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dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
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dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
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wtfile
proc ft
fn not used
math f
werr
wexp
wbs
wnt wft
* Impurities
7
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1.01
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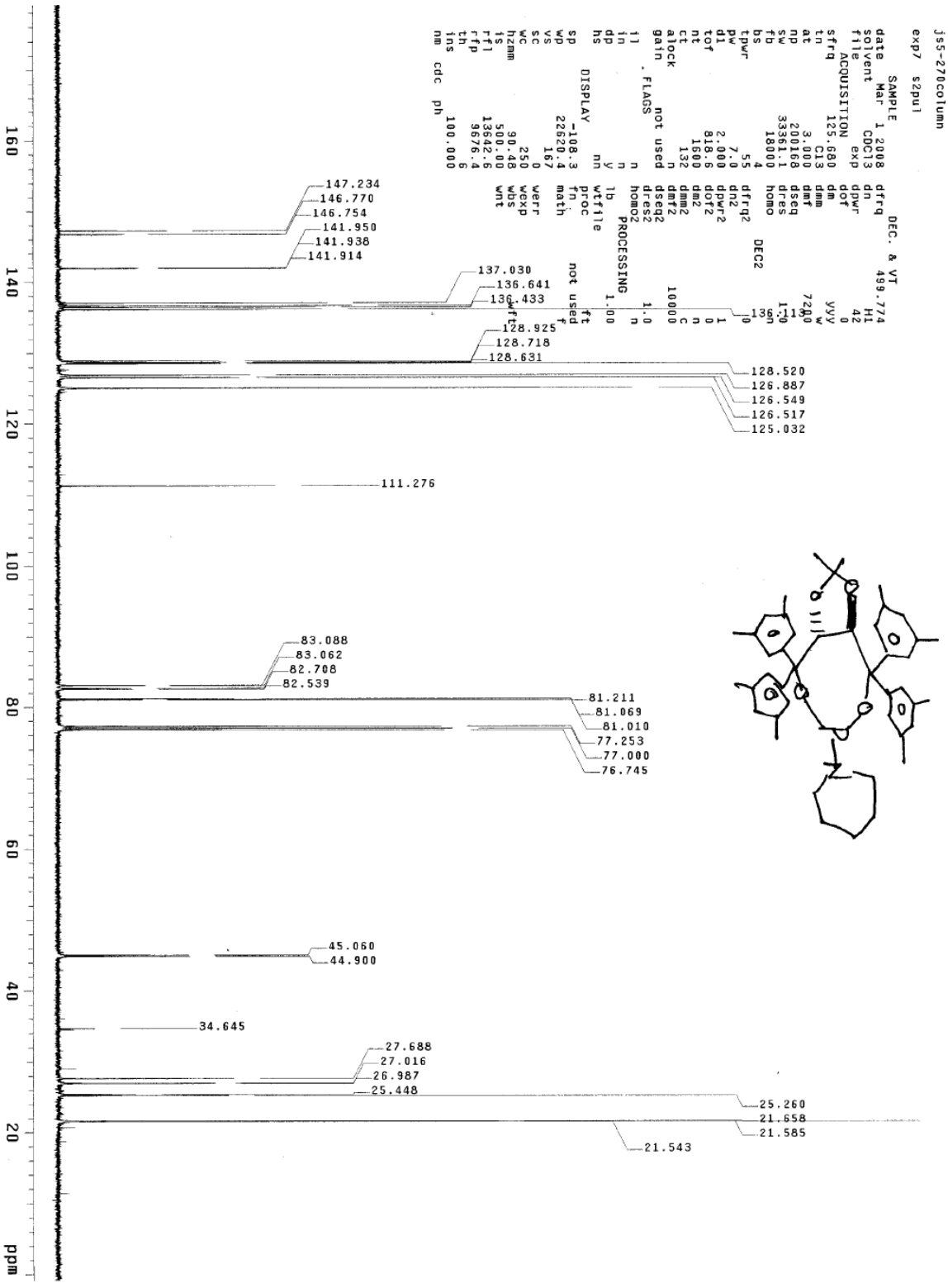
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in n
dp y
hs nn
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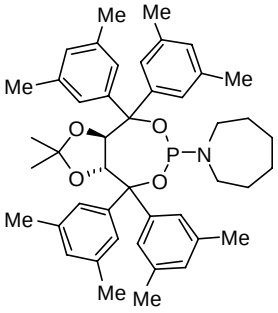
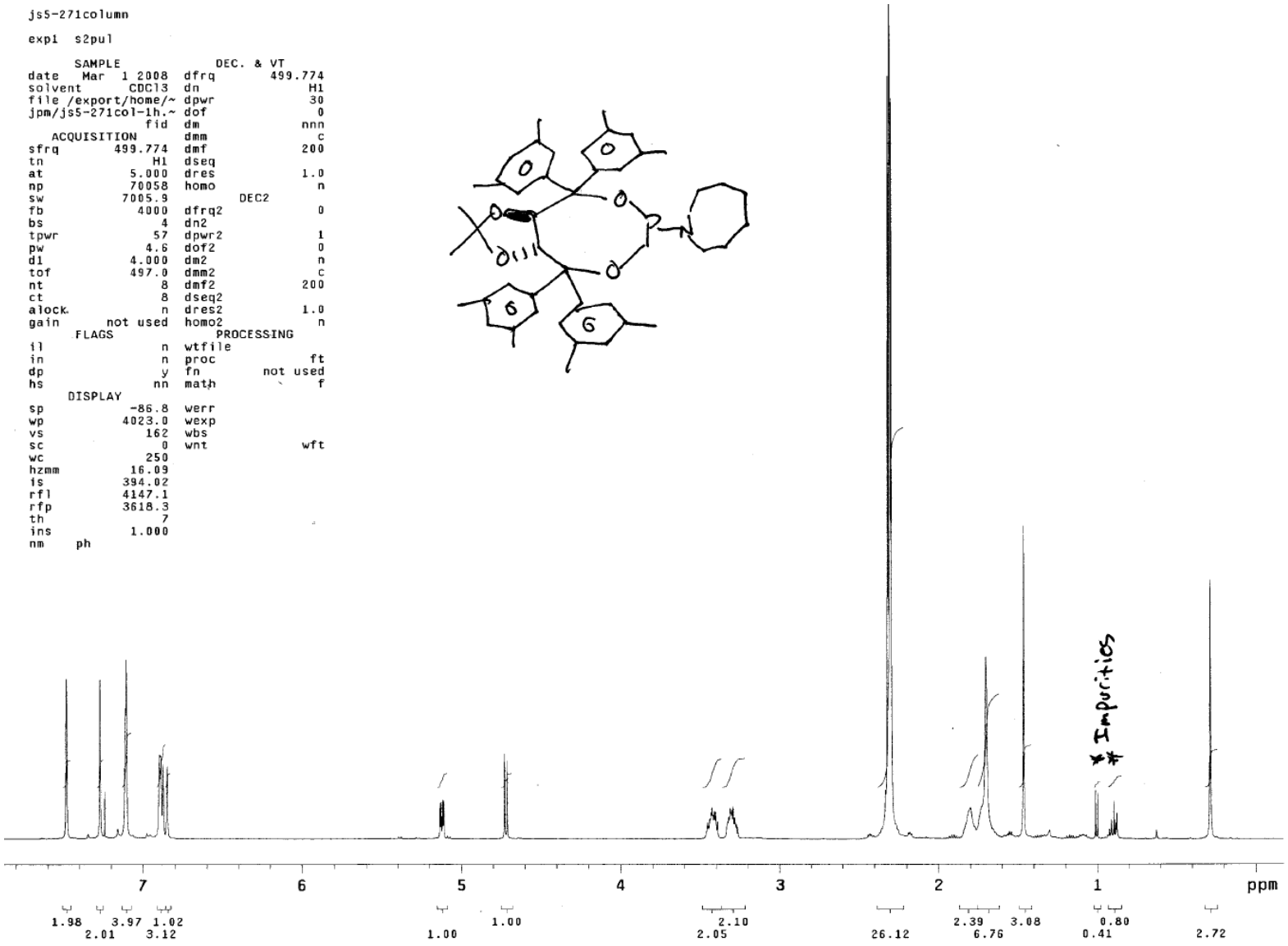


[3,5-xylylTADDOL]PNC$_6$H$_{12}$ (2.160). Prepared in 59% yield according to the procedure used to synthesize **2.112** on page 198. A white solid. R_f = 0.15 (SiO_2, 30:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3000 (m), 2920 (s), 2852 (s), 1603 (s), 1459 (s), 1379 (s), 1244 (m), 1215 (s), 1164 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.48 (2H, s), 7.27 (2H, s), 7.11 (2H, s), 7.10 (2H, s), 6.89 (2H, s), 6.87 (1H, s), 6.85 (1H, s), 5.12 (1H, dd, *J* = 8.5 Hz, *J* = 3.5 Hz), 4.72 (1H, d, *J* = 8.5 Hz), 3.37-3.47 (2H, m), 3.25-3.35 (2H, m), 2.318 (6H, s), 2.308 (6H, s), 2.304 (6H, s), 2.296 (6H, s), 1.62-1.87 (8H, m), 1.46 (3H, s), 0.29 (3H, s); ^{13}C NMR ($CDCl_3$): δ 147.3, 146.82, 146.80, 137.0, 136.6, 136.5, 136.1, 128.9, 128.7, 128.6, 128.5, 127.0, 126.51, 126.48, 125.08, 125.06, 111.2, 83.27, 83.24, 82.70, 82.53, 81.19, 81.12, 80.84, 46.83 (d, $^2J_{CP}$ = 21 Hz), 34.65, 31.30 (d, $^3J_{CP}$ = 3.3 Hz), 27.74, 27.03, 25.34, 25.26, 21.65, 21.60, 21.55, 21.53. ^{31}P NMR ($CDCl_3$): δ 140.9. LRMS (ESI+) Calcd for $C_{45}H_{56}NO_4P$ $(M + H)^+$: 706.4, Found $(M + H)^+$: 706.5. $[\alpha]_D^{20}$ = -112° (*c* = 2.6, $CHCl_3$).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is 394.02
rfl 4147.1
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dseq
dres 1.0
homo n
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dpwr2 1
dof2 0
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dmm2 c
dmf2 200
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dres2 1.0
homo2 n
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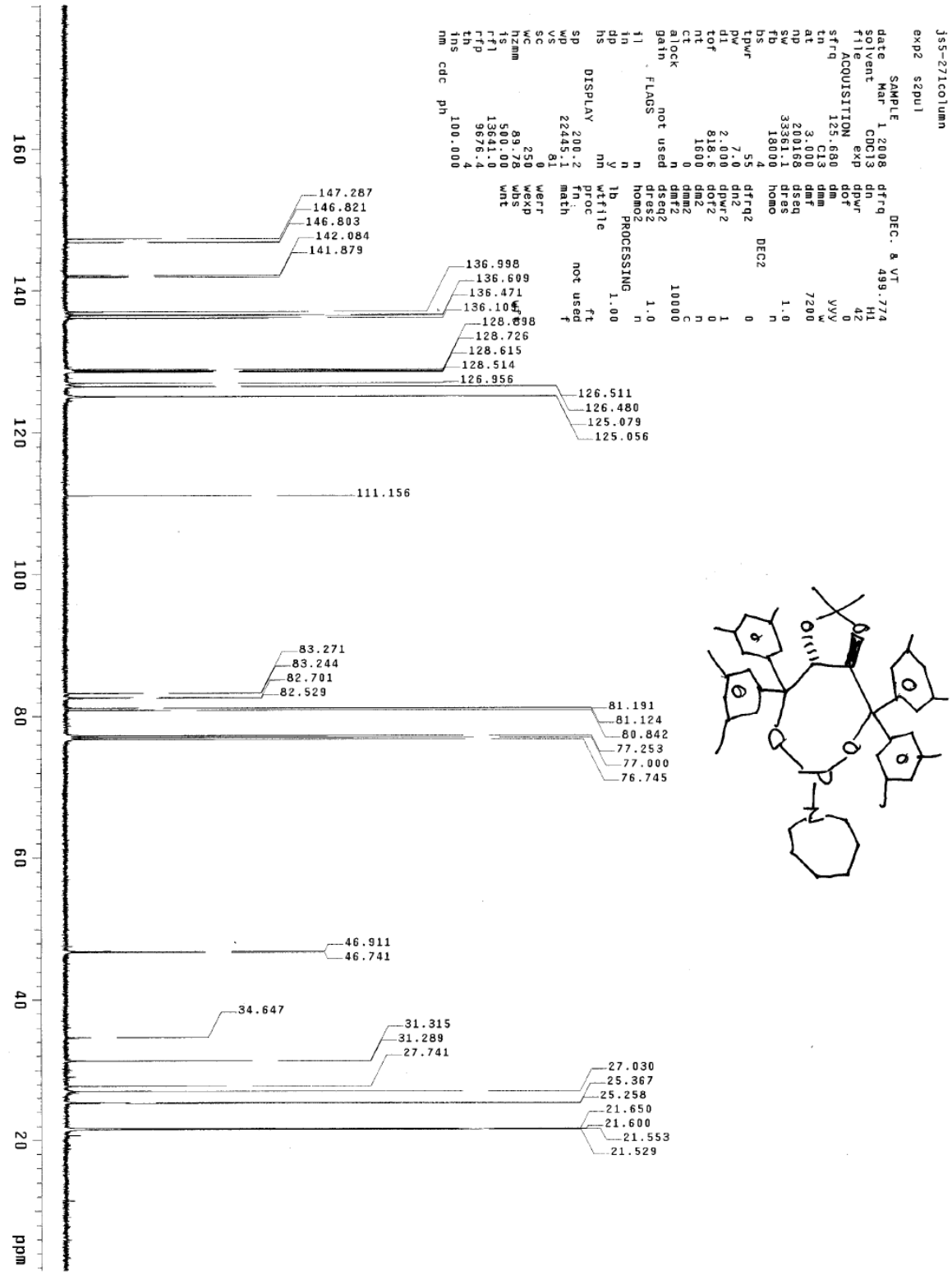
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date Mar 1 2008
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pw 7.0
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tof 818.6
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ct 0
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gain not used
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dp n
hs nn
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sc 0
wc 250
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is 500.00
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rfp 9676.4
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dm y
dmm w
dmf 7200
dseq
dres 1.0
homo n
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dpwr2 1
dof2 0
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dmm2 c
dmf2 10000
dseq2
dres2 1.0
homo2 n
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wbs
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125.056
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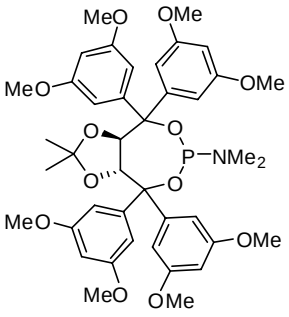
ppm



[3,5-(MeO)$_2$TADDOL]PNMe$_2$ (2.201). Prepared in 75% yield according to the procedure used to synthesize **2.112** on page 198. A white solid. R_f = 0.19 (SiO_2, 2:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3093 (w), 3000 (m), 2937 (m), 2831 (m), 2797 (w), 1594 (s), 1459 (s), 1421 (s), 1379 (m), 1350 (s), 1312 (s), 1286 (s), 1201 (s), 1151 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.96 (2H, d, *J* = 2.0 Hz), 6.80 (2H, d, *J* = 2.5 Hz), 6.69 (2H, d, *J* = 2.5 Hz), 6.67 (2H, d, *J* = 2.5 Hz), 6.30-6.36 (3H, m), 6.29 (1H, t, *J* = 2.0 Hz), 5.11 (1H, dd, *J* = 8.5 Hz, *J* = 3.5 Hz), 4.67 (1H, d, *J* = 8.5 Hz), 3.73 (6H, s), 3.719 (6H, s), 3.717 (6H, s), 3.708 (6H, s), 2.79 (6H, d, *J* = 11 Hz), 1.40 (3H, s), 0.38 (3H, s); ^{13}C NMR ($CDCl_3$): δ 160.3, 159.96, 159.91, 159.59, 149.1, 148.4, 143.8, 143.6, 111.3, 107.8, 107.15, 107.12, 105.74, 105.66, 99.34, 98.85, 98.50, 98.43, 83.02, 82.99, 82.69, 82.52, 81.13, 81.08, 81.00, 55.28, 55.20, 55.14, 35.37 (d, $^2J_{CP}$ = 20 Hz), 27.71, 25.30. ^{31}P NMR ($CDCl_3$): δ 140.6. LRMS (ESI+) Calcd for $C_{41}H_{50}NO_{12}P$ $(M + H)^+$: 780.3, Found $(M + H)^+$: 780.3. $[\alpha]_D^{20}$ = -95^o (*c* = 2.6, $CHCl_3$).

js4-204column

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sw	7005.9	dres	1.0
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ct	8	dmm2	c
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in	n	PROCESSING	
dp	y	wtfile	
hs	nn	proc	ft
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sc	0	wexp	
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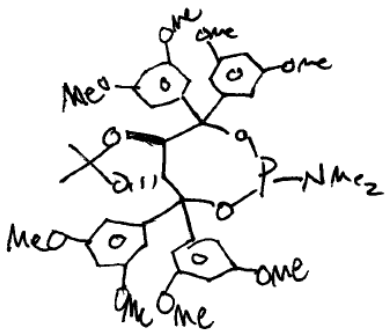
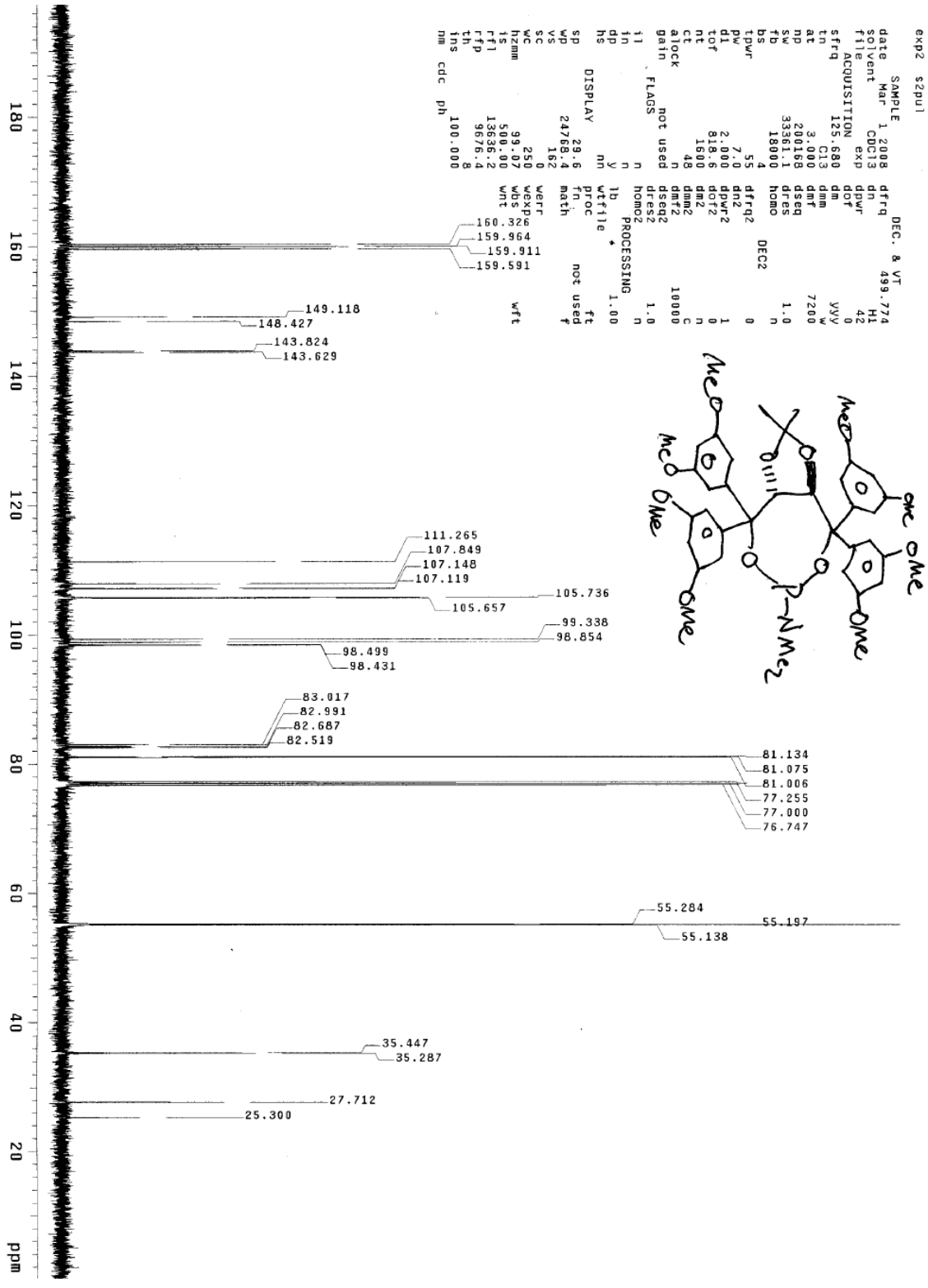
nm	ph		

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solvent CDCl3
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tof 818.6
nt 1600
ct 48
alock n
gain not used
FLAGS
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in n
dp y
hs nn
DISPLAY
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vs 162
sc 0
wc 250
hzmm 99.07
is 500.00
rfl 13636.2
rfp 9676.4
th 8
ins 100.000
nm cdc ph
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wbs
wnt
wexp
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dn2
dpwr2
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dmf2
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dres2
homo2
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homo n
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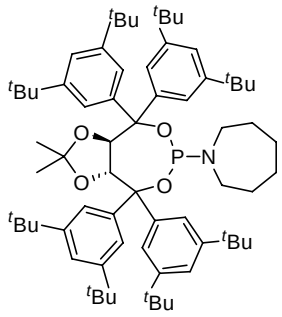
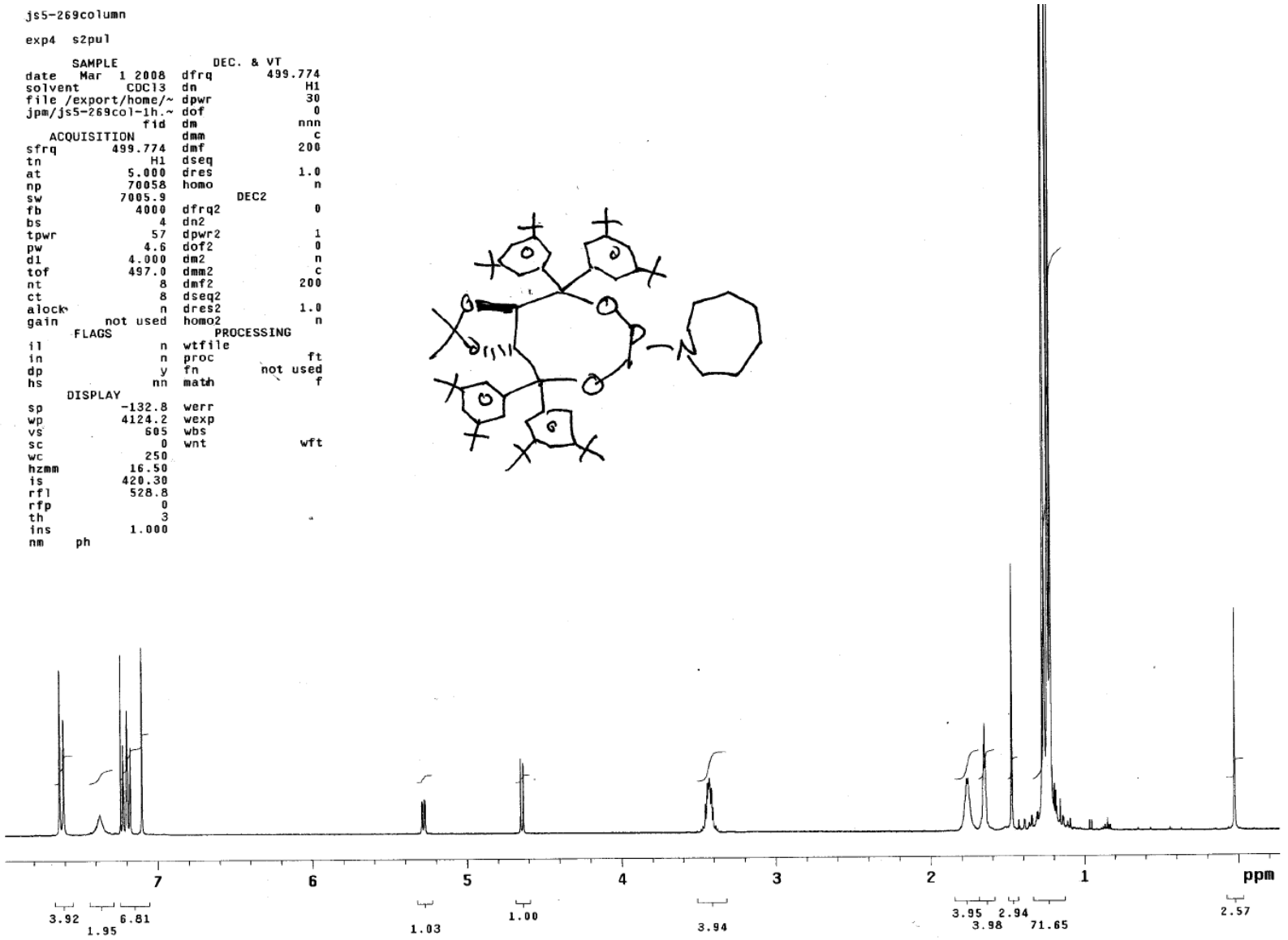
ppm



[3,5-(^{t}Bu)$_2$TADDOL]PNC$_6$H$_{12}$ (2.161). Prepared in 88% yield according to the procedure used to synthesize **2.112** on page 198. A white solid. R_f = 0.38 (SiO_2, 55:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3084 (w), 2958 (s), 2907 (s), 2860 (m), 1599 (m), 1480 (m), 1451 (m), 1396 (m), 1362 (m), 1244 (m), 1198 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.63 (2H, d, *J* = 1.5 Hz), 7.61 (2H, d, *J* = 1.5 Hz), 7.37 (2H, br s), 7.22 (1H, t, *J* = 2.0 Hz), 7.19-7.21 (2H, m), 7.18 (1H, t, *J* = 2.0 Hz), 7.10 (2H, d, *J* = 1.5 Hz), 5.28 (1H, dd, *J* = 9.0 Hz, *J* = 2.5 Hz), 4.64 (1H, d, *J* = 9.0 Hz), 3.36-3.49 (4H, m), 1.70-1.82 (4H, m), 1.62-1.69 (4H, m), 1.47 (3H, s), 1.27 (18H, s), 1.26 (18H, s), 1.24 (18H, s), 1.22 (18H, s), 0.027 (3H, s); ^{13}C NMR ($CDCl_3$): δ 149.5, 149.1, 148.7, 148.6, 146.6, 146.3, 142.2, 141.2, 123.7, 122.0, 121.5, 120.6, 120.12, 119.99, 119.88, 109.6, 83.92, 83.89, 83.78, 83.64, 82.45, 82.39, 80.75, 80.71, 46.76 (d, $^2J_{CP}$ = 21 Hz), 34.96, 34.88, 34.75, 31.59 (d, $^3J_{CP}$ = 4.0 Hz), 31.59, 31.43, 28.02, 27.10, 23.77. ^{31}P NMR ($CDCl_3$): δ 141.5. LRMS (ESI+) Calcd for $C_{69}H_{104}NO_4P$ $(M + H)^+$: 1042.8, Found $(M + H)^+$: 1043.3. $[\alpha]_D^{20}$ = -37^o (*c* = 2.0, $CHCl_3$).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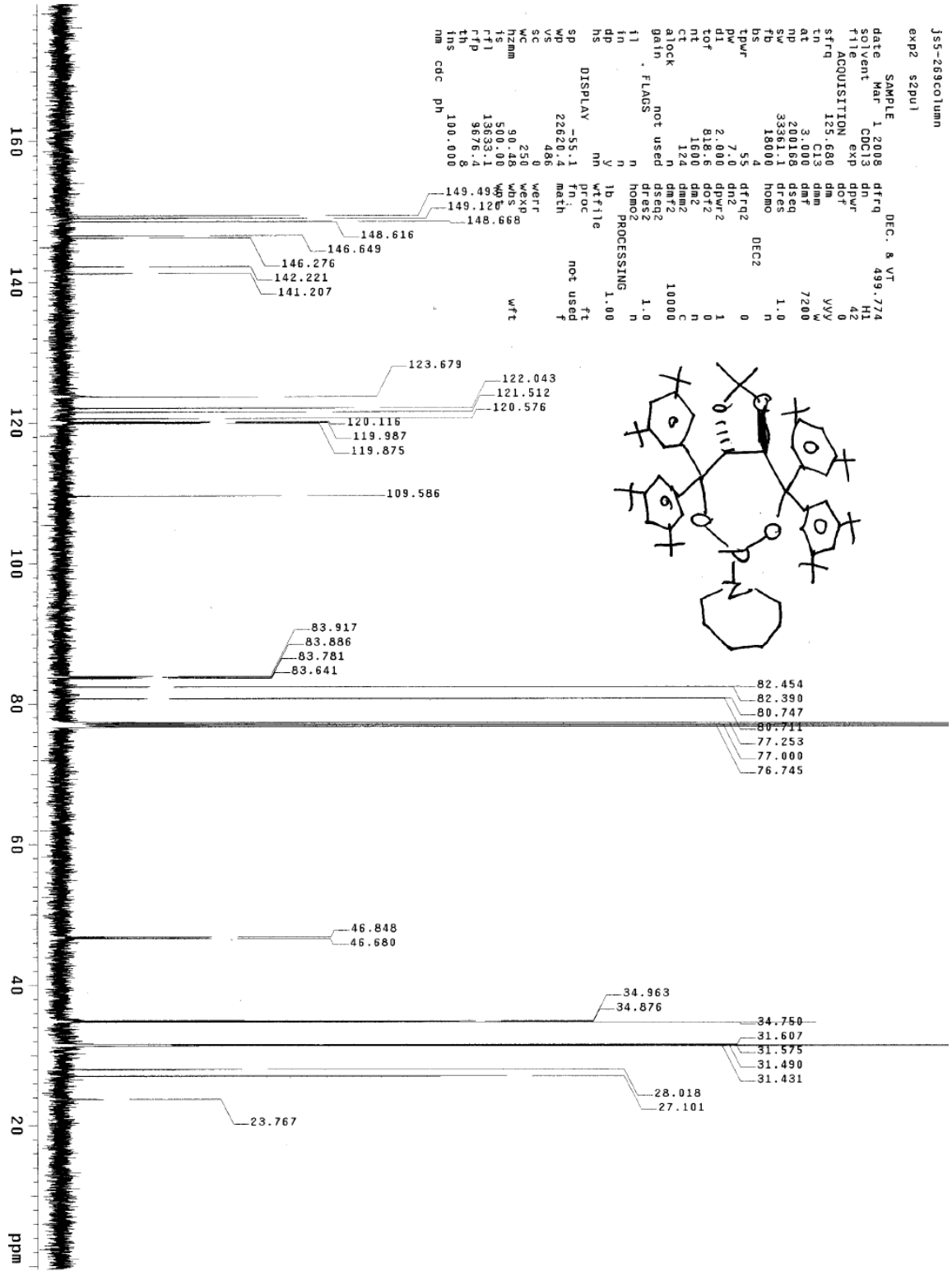
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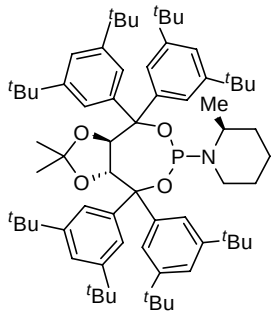
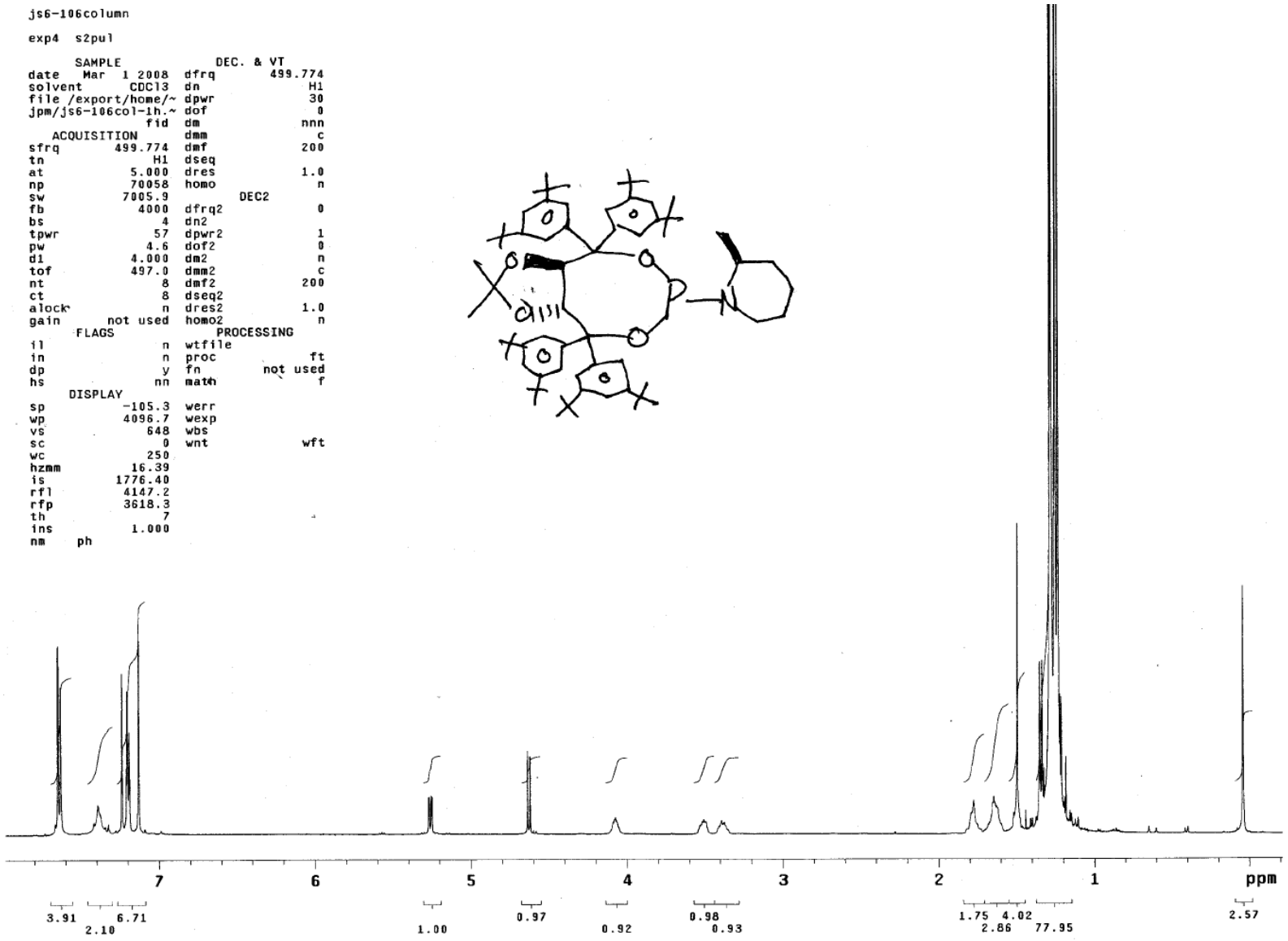


[3,5-(^{t}Bu)$_2$TADDOL]PNC$_6$H$_{12}$ (2.162). Prepared in 86% yield according to the procedure used to synthesize **2.112** on page 198 using 1.5 equiv of (*S*)-(+)-2-methylpiperidine. A white solid. R_f = 0.42 (SiO_2, 30:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3076 (w), 2962 (s), 2907 (s), 2861 (m), 1599 (m), 1472 (m), 1388 (m), 1362 (m), 1248 (m), 1206 (m), 1160 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.65 (2H, d, *J* = 2.0 Hz), 7.63 (2H, d, *J* = 1.5 Hz), 7.34-7.46 (2H, m), 7.24 (1H, t, *J* = 1.5 Hz), 7.17-7.22 (3H, m), 7.13 (2H, d, *J* = 2.0 Hz), 5.26 (1H, dd, *J* = 8.5 Hz, *J* = 2.5 Hz), 4.63 (1H, d, *J* = 8.5 Hz), 4.01-4.15 (1H, m), 3.45-3.57 (1H, m), 3.32-3.44 (1H, m), 1.72-1.85 (2H, m), 1.56-1.72 (3H, m), 1.49 (4H, s), 1.29 (18H, s), 1.28 (18H, s), 1.25 (18H, s), 1.23 (18H, s), 0.042 (3H, s); ^{13}C NMR ($CDCl_3$): δ 149.5, 149.1, 148.66, 148.61, 146.6, 146.3, 142.3, 141.4, 123.7, 122.0, 121.6, 120.5, 120.1, 119.9, 119.8, 109.4, 83.90, 83.87, 83.70, 83.56, 82.52, 82.45, 80.59, 80.56, 47.62 (d, $^2J_{CP}$ = 20 Hz), 39.90 (d, $^2J_{CP}$ = 19 Hz), 34.96, 34.88, 34.76, 34.75, 32.69, 31.53, 31.49, 31.58, 31.44, 28.04, 27.58, 23.80, 20.75, 18.68, 18.60. ^{31}P NMR ($CDCl_3$): δ 137.6. LRMS (ESI+) Calcd for $C_{69}H_{104}NO_4P$ $(M + H)^+$: 1042.8, Found $(M + H)^+$: 1043.3. $[\alpha]_D^{20}$ = -23° (*c* = 2.3, $CHCl_3$).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date Mar 1 2008
solvent CDCl3
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dp y
hs nn
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rfp 3618.3
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dmf 200
dseq
dres 1.0
homo n
DEC2
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dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
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dseq2
dres2 1.0
homo2 n
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wexp
wbs
wnt wft
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3
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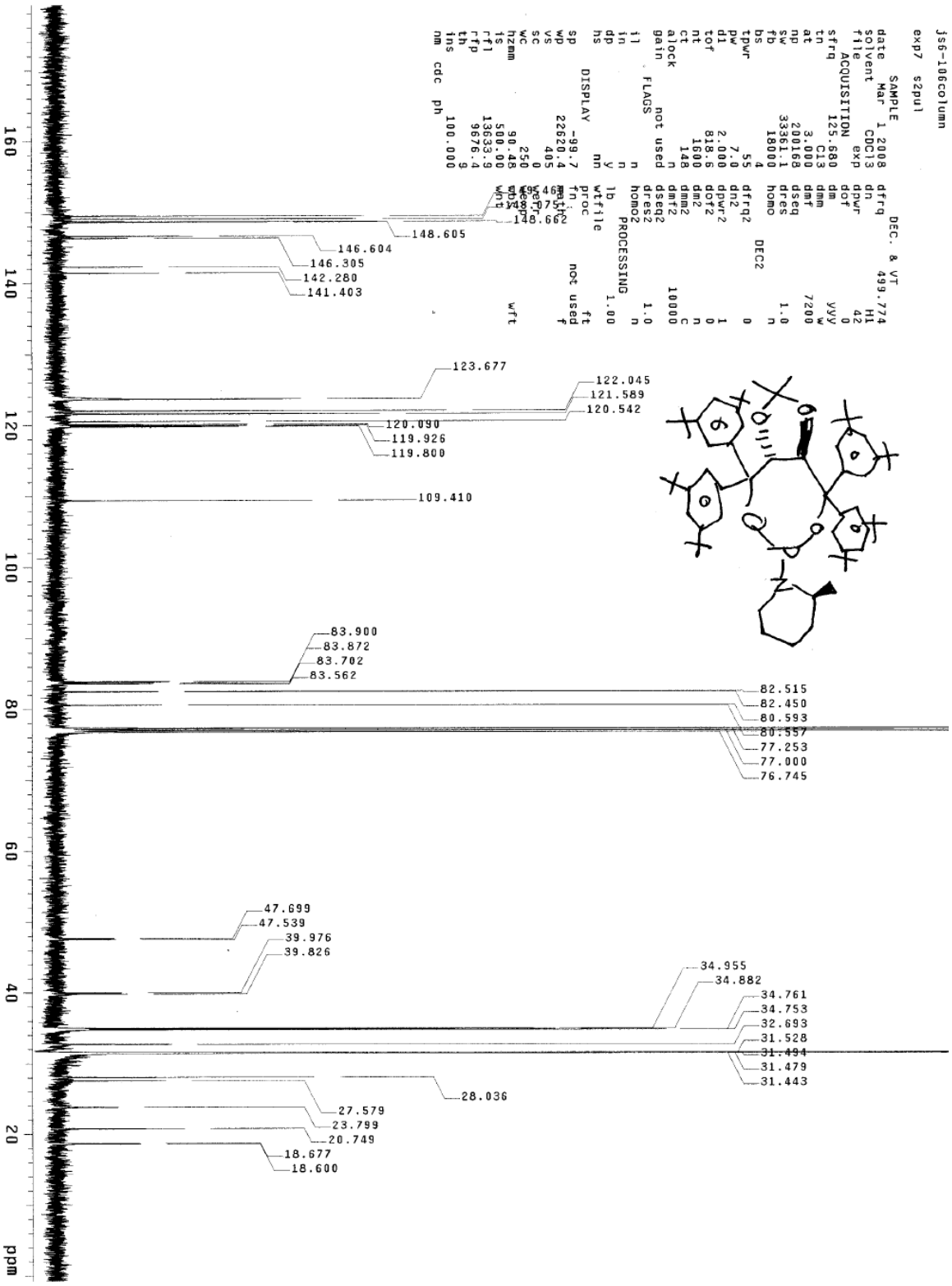
2.86
77.95
2.57


js6-106column
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date Mar 1 2008
solvent CDCl3
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ct 1600
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gain not used
FLAGS
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dp y
hs nn
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dmf 7200
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dres 1.0
homo n
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dn2
dpwr2
dof2
dm2
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dmf2 c
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homo2 1.0
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122.045
121.589
120.542
120.090
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77.253
77.000
76.745
47.699
47.539
39.976
39.826
34.955
34.882
34.761
34.753
32.693
31.528
31.494
31.479
31.443
28.036
27.579
23.799
20.749
18.677
18.600
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140
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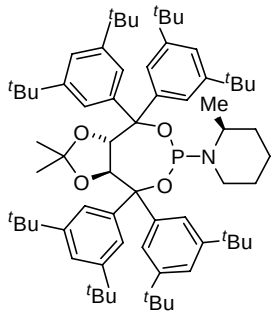
60
40
20
ppm



[3,5-(^{t}Bu)$_2$TADDOL]PNC$_6$H$_{12}$ (2.163). Prepared in 96% yield according to the procedure used to synthesize **2.112** on page 198 using 1.5 equiv of (*S*)-(+)-2-methylpiperidine. A white solid. R_f = 0.47 (SiO_2, 30:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3075 (w), 2962 (s), 2911 (s), 2865 (m), 1599 (m), 1480 (m), 1396 (m), 1379 (m), 1362 (s), 1252 (s), 1201 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.71 (2H, d, *J* = 2.0 Hz), 7.67 (2H, d, *J* = 1.5 Hz), 7.48 (2H, br s), 7.22-7.28 (4H, m), 7.18 (2H, d, *J* = 2.0 Hz), 5.26 (1H, dd, *J* = 8.5 Hz, *J* = 2.5 Hz), 4.63 (1H, d, *J* = 8.5 Hz), 4.28-4.38 (1H, m), 3.49-3.60 (1H, m), 3.31 (1H, app q, *J* = 12 Hz), 1.91-2.01 (1H, m), 1.72-1.85 (1H, m), 1.63-1.72 (2H, m), 1.50-1.63 (5H, m), 1.321 (18H, s), 1.318 (18H, s), 1.299 (18H, s), 1.277 (18H, s), 0.078 (3H, s); ^{13}C NMR ($CDCl_3$): δ 149.4, 149.1, 148.7, 146.7, 146.59, 146.47, 142.3, 141.1, 123.7, 122.0, 121.5, 120.5, 120.1, 119.9, 109.5, 84.12, 84.09, 84.04, 83.90, 82.21, 82.14, 80.49, 80.46, 46.64 (d, $^2J_{CP}$ = 15 Hz), 39.96 (d, $^2J_{CP}$ = 27 Hz), 34.98, 34.88, 34.79, 34.77, 32.21, 31.51, 31.45, 28.10, 27.69, 23.76, 20.36, 18.09, 18.05. ^{31}P NMR ($CDCl_3$): δ 138.0. LRMS (ESI+) Calcd for $C_{69}H_{104}NO_4P$ $(M + H)^+$: 1042.8, Found $(M + H)^+$: 1043.4. $[\alpha]_D^{20}$ = +29° (*c* = 3.4, $CHCl_3$).

JS6-107c01

STANDARD PROTON PARAMETERS

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sw	7005.9	dres	1.0
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bs	4	DEC2	
tpwr	57	dfrq2	0
pw	4.6	dn2	
d1	4.000	dpwr2	1
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ct	8	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	PROCESSING	
dp	y	wtfile	
hs	nn	proc	ft
DISPLAY		fn	not used
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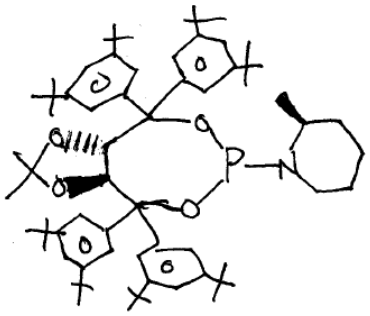
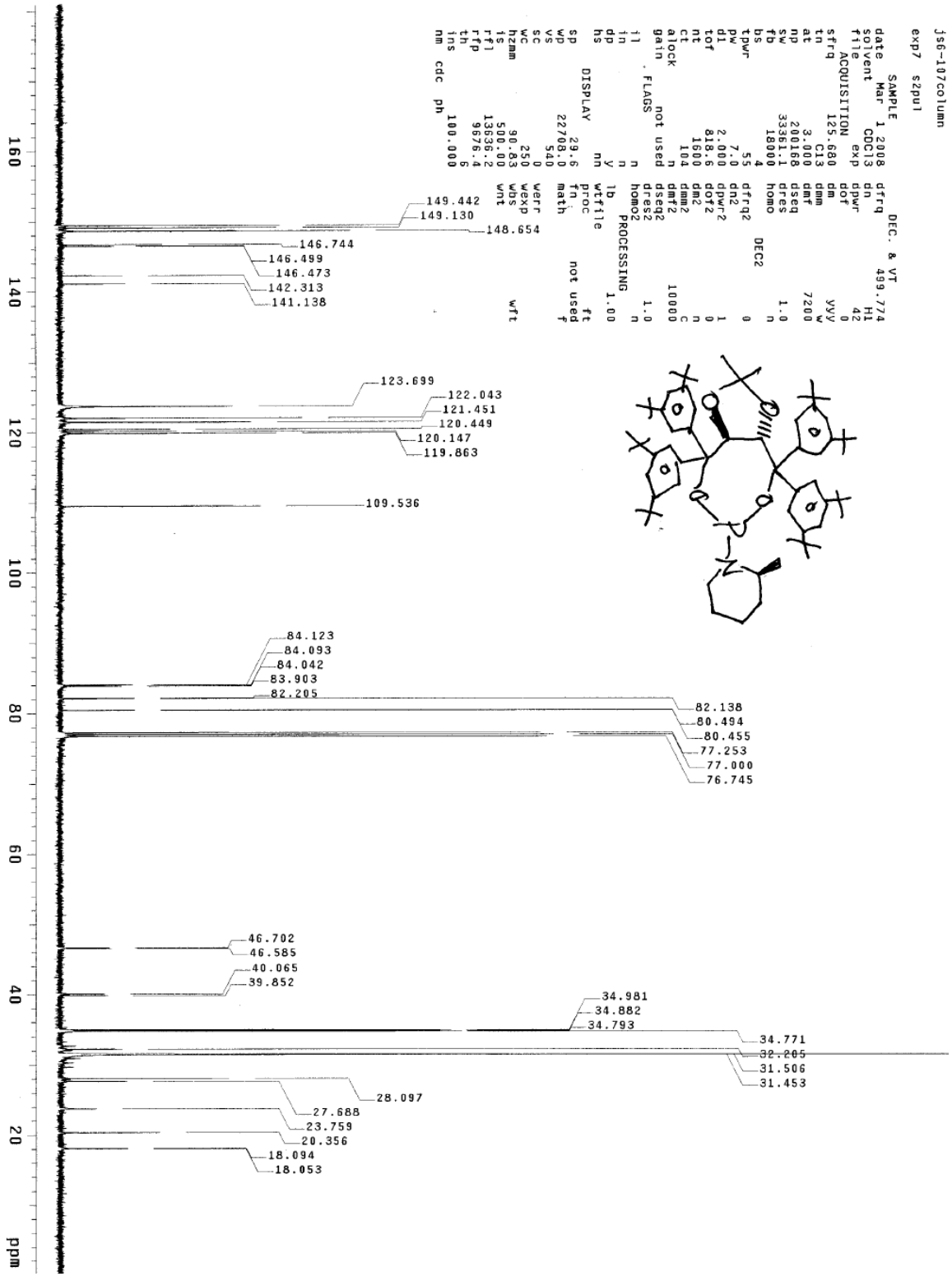
nm	ph		

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d1 2.000
tof 818.6
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ct 104
alock n
gain not used
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in n
dp y
hs nn
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hzmm 90.83
is 500.00
rfl 13636.2
rfp 9676.4
th 6
ins 100.000
nm cdc ph
wft
wfm
wexp
wbs
wnt
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dof 42
dm w
dmm w
dmf 7200
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dres 1.0
homo
DEC2
dfrq2
dn2
dpwr2
dof2
dm2
dmm2
dmf2
dseq2
dres2 1.0
homo2
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146.499
146.473
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84.093
84.042
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82.205
82.138
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80.455
77.253
77.000
76.745
46.702
46.585
40.065
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31.506
31.453
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23.759
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140
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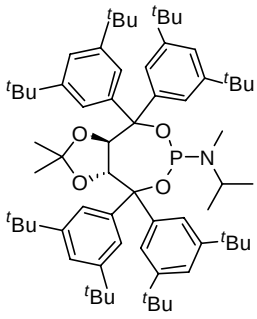
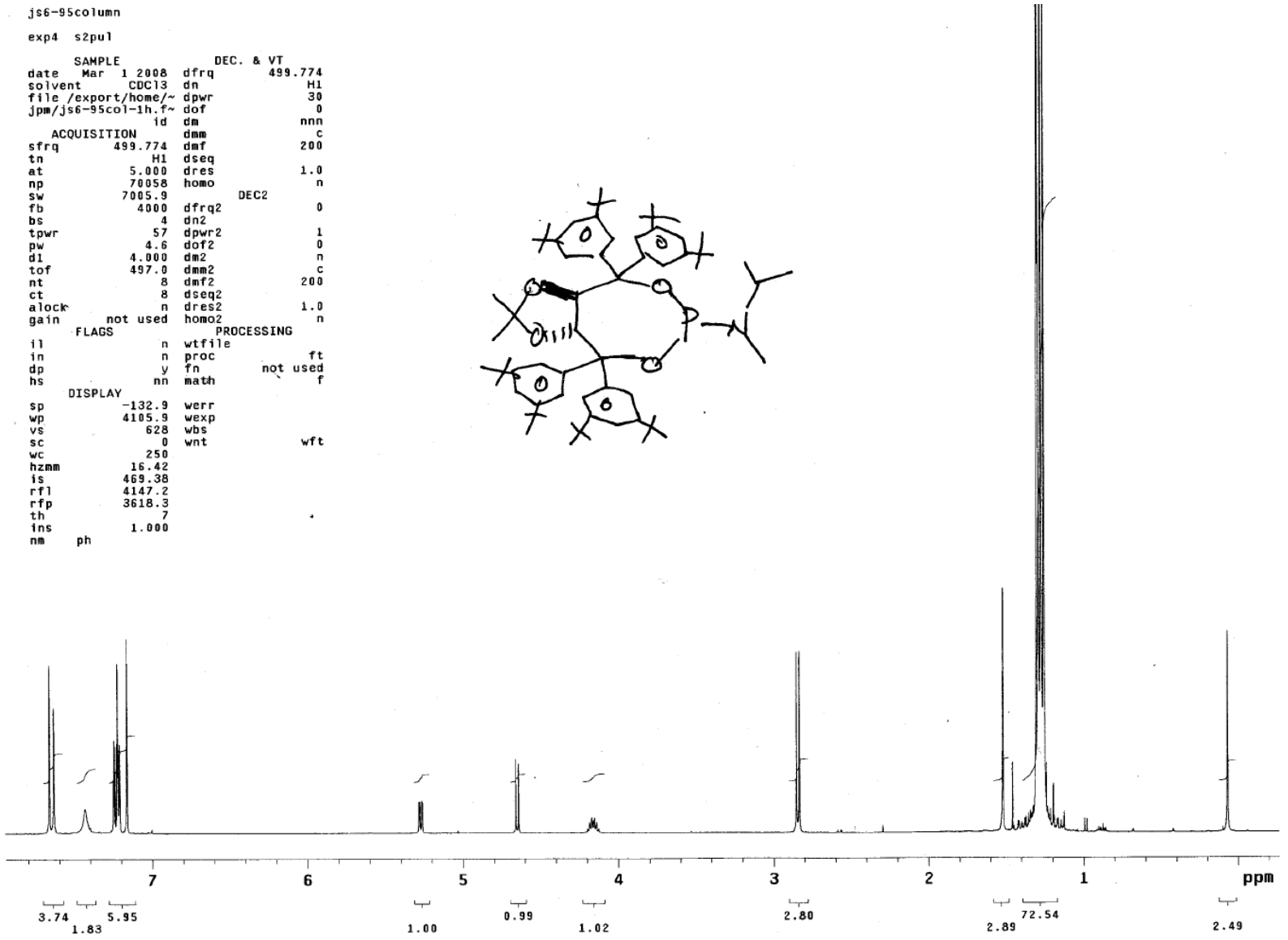
60
40
20
ppm



[3,5-(^{t}Bu)$_2$TADDOL]PN(Me)^{i}Pr (2.166). Prepared in 48% yield according to the procedure used to synthesize **2.112** on page 198. A white solid. R_f = 0.43 (SiO_2, 50:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3080 (w), 2962 (s), 2907 (s), 2865 (m), 1599 (m), 1476 (m), 1455 (m), 1438 (m), 1388 (m), 1358 (s), 1248 (s), 1201 (m), 1164 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.66 (2H, d, *J* = 2.0 Hz), 7.64 (2H, d, *J* = 1.5 Hz), 7.44 (2H, br s), 7.25 (1H, t, *J* = 1.5 Hz), 7.23 (2H, t, *J* = 1.5 Hz), 7.21 (1H, t, *J* = 2.0 Hz), 5.27 (1H, dd, *J* = 8.5 Hz, *J* = 3.0 Hz), 4.65 (1H, d, *J* = 8.5 Hz), 4.10-4.22 (1H, m), 2.84 (3H, d, *J* = 9.5 Hz), 1.52 (3H, s), 1.23-1.34 (78H, m), 0.069 (3H, s); ^{13}C NMR ($CDCl_3$): δ 149.5, 149.1, 148.67, 148.64, 146.6, 146.39, 146.36, 142.3, 141.2, 123.67, 123.65, 122.0, 121.5, 120.5, 120.1, 119.89, 119.85, 109.6, 83.96, 83.93, 83.88, 83.75, 82.35, 82.29, 80.56, 80.53, 46.57 (d, $^2J_{CP}$ = 26 Hz), 34.97, 34.88, 34.77, 31.50, 31.45, 30.33, 28.06, 25.16 (d, $^2J_{CP}$ = 19 Hz), 23.81, 21.55 (d, $^3J_{CP}$ = 7.0 Hz), 21.24, 21.22. ^{31}P NMR ($CDCl_3$): δ 141.4. LRMS (ESI+) Calcd for $C_{67}H_{102}NO_4P$ $(M + H)^+$: 1016.8, Found $(M + H)^+$: 1017.3. $[\alpha]_D^{20}$ = -27^o (*c* = 3.0, $CHCl_3$).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solvent CDCl3
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ct 8
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dp y
hs nn
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rfp 3618.3
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dmf 200
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dres 1.0
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dmf2 200
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homo2 n
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wexp
wbs
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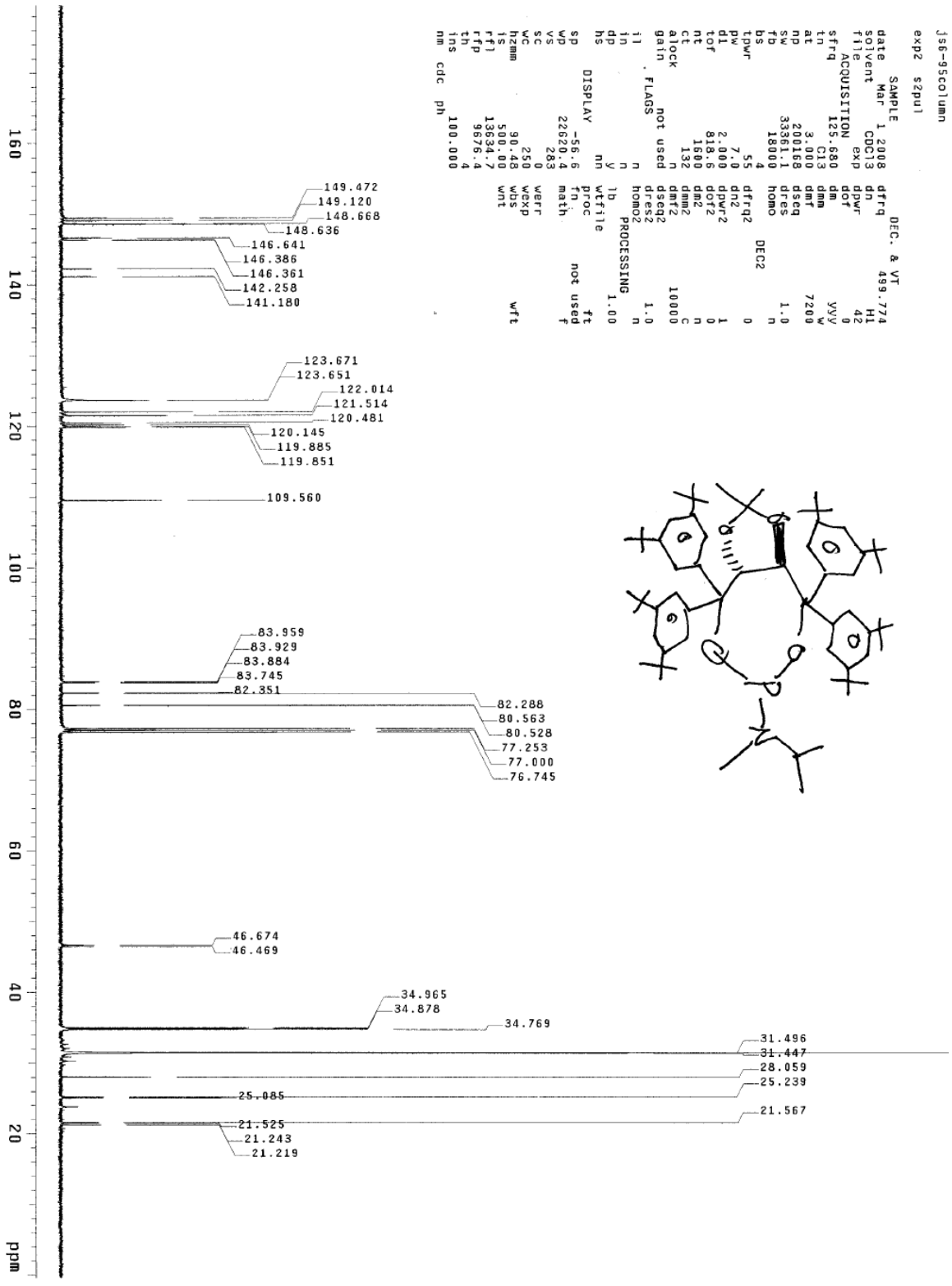
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date Mar 1 2008
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ct 132
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gain not used
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dp y
hs nn
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rfl 9676.4
rfp 4
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homo
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dres2 1.0
homo2 n
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80.528
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77.000
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46.469
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31.447
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21.525
21.243
21.219
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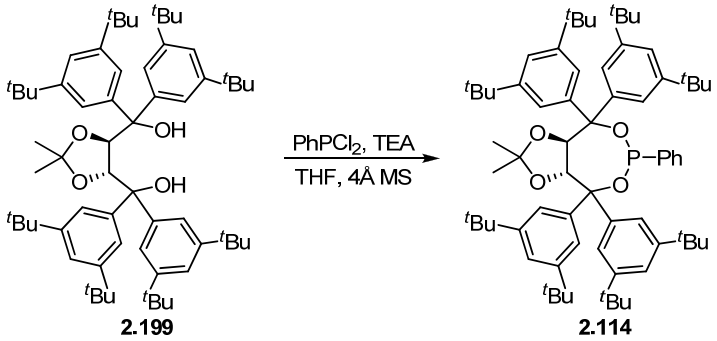
140
120
100
80
60
40
20
ppm

Phosphonite ligand syntheses:

Phosphonites were prepared by the addition of dichlorophenylphosphine to the appropriate TADDOL derivative with TEA as a base. Ligand **2.115**[73] has been prepared previously.

Synthesis of 2.114



To a mixture of 0.898 g (0.981 mmol) of **2.199** and 4 Å molecular sieves in 3.9 mL of THF at 0 ^{o}C was added 0.32 ml (2.3 mmol) of TEA. Next, 150 μL (1.08 mmol) of dichlorophenylphosphine was added dropwise. The reaction was allowed to warm to room temperature and allowed to stir for 2 h. The reaction was diluted with Et_2O, filtered through celite, and concentrated under reduced pressure. Column chromatography (SiO_2, hexanes:EtOAc) afforded 0.726 g (0.711 mmol, 72%) of **2.114** as a white solid.

[3,5-(^{t}Bu)$_2$TADDOL]PPh (2.114). Mp 240-260 ^{o}C (decomp.). R_f = 0.40 (SiO_2, 30:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3075 (m), 2968 (s), 2873 (s), 1797 (w), 1595 (s), 1482 (s), 1369 (s), 1249 (s), 1205 (s), 1167 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.96-8.30 (2H, m), 7.67 (2H, s), 7.55 (2H, s), 7.38-7.53 (5H, m), 7.26 (2H, d, *J* = 6.5 Hz), 7.21 (2H, d, *J*

= 7.5 Hz), 7.14 (2H, s), 5.60 (1H, dd, *J* = 8.8 Hz, *J* = 3.5 Hz), 4.89 (1H, d, *J* = 8.8 Hz), 1.56 (3H, s) 1.20-1.33 (72H, m), 0.11 (3H, s); ^{13}C NMR ($CDCl_3$): δ 149.8, 149.5, 148.9, 148.8, 146.3, 145.6, 145.5, 142.6, 142.5, 141.6, 140.6, 130.5, 130.1, 129.9, 128.2, 128.1, 123.8, 122.3, 121.6, 120.7, 120.43, 120.38, 120.2, 84.39, 84.36, 84.24, 84.18, 84.09, 83.94, 83.17, 83.13, 35.02, 34.88, 34.77, 34.75, 31.53, 31.48, 31.45, 31.41, 28.09, 23.68. ^{31}P NMR ($CDCl_3$): δ 154.3. LRMS (ESI+) Calcd for $C_{69}H_{97}O_4P$ $(M + Na + H)^+$: 1044.7, Found $(M + Na + H)^+$: 1044.6. $[\alpha]_D^{20} = -44^o$ (*c* = 0.5, $CHCl_3$).

js4-287column

exp1 s2pul

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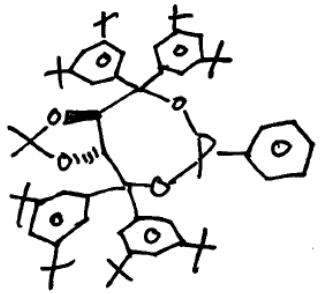
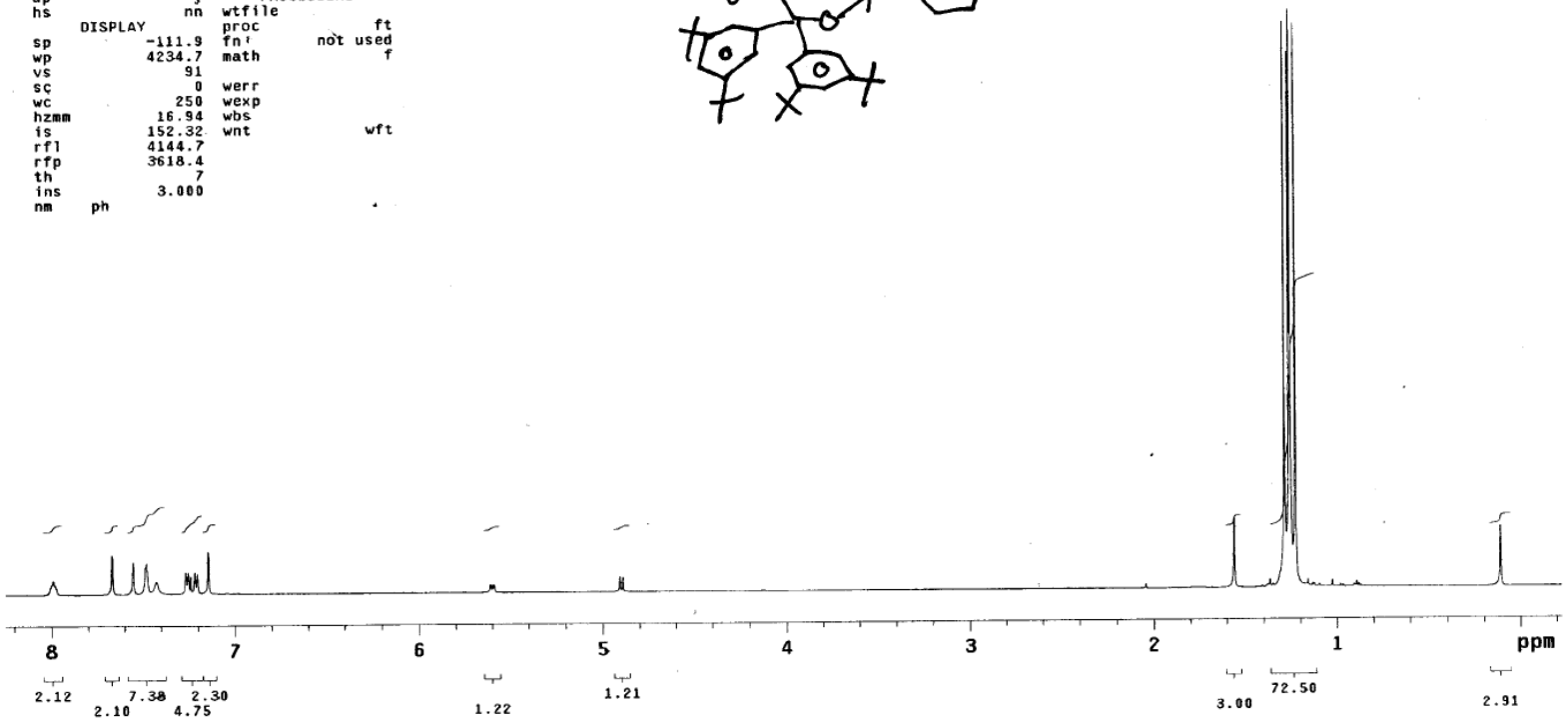
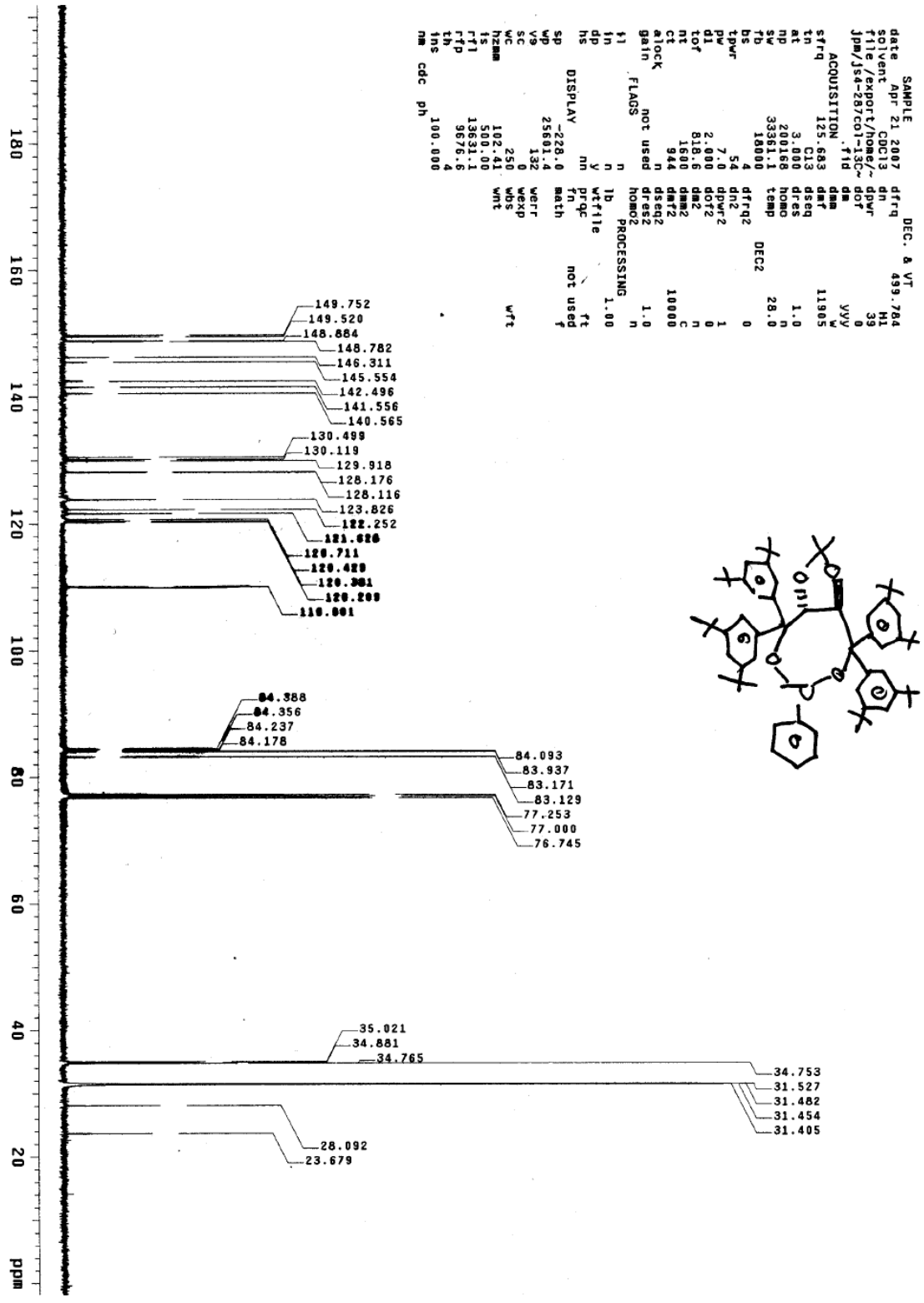
sw	7005.9	dres	1.0
fb	4000	homo	n
bs	4	temp	28.0
tpwr	56	DEC2	
pw	4.6	dfrq2	0
d1	4.000	dn2	
tof	497.0	dpwr2	1
nt	8	dof2	0
ct	8	dm2	n
alock	n	dmm2	c
gain	not used	dmf2	200
FLAGS		dseq2	
il	n	dres2	1.0
in	n	homo2	n
dp	y	PROCESSING	
hs	nn	wtfile	
DISPLAY		proc	ft
sp	-111.9	fn	not used
wp	4234.7	math	f
vs	91		
sc	0	werr	
wc	250	wexp	
hzmm	16.94	wbs	
is	152.32	wnt	wft
rfl	4144.7		
rfp	3618.4		
th	7		
ins	3.000		
nm	ph		



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date Apr 21 2007
solvent CDCl3
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jpm/js4-287col-13C~
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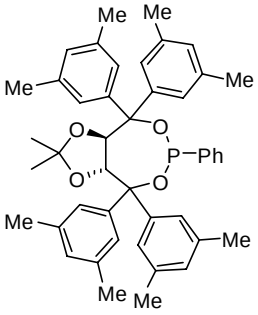
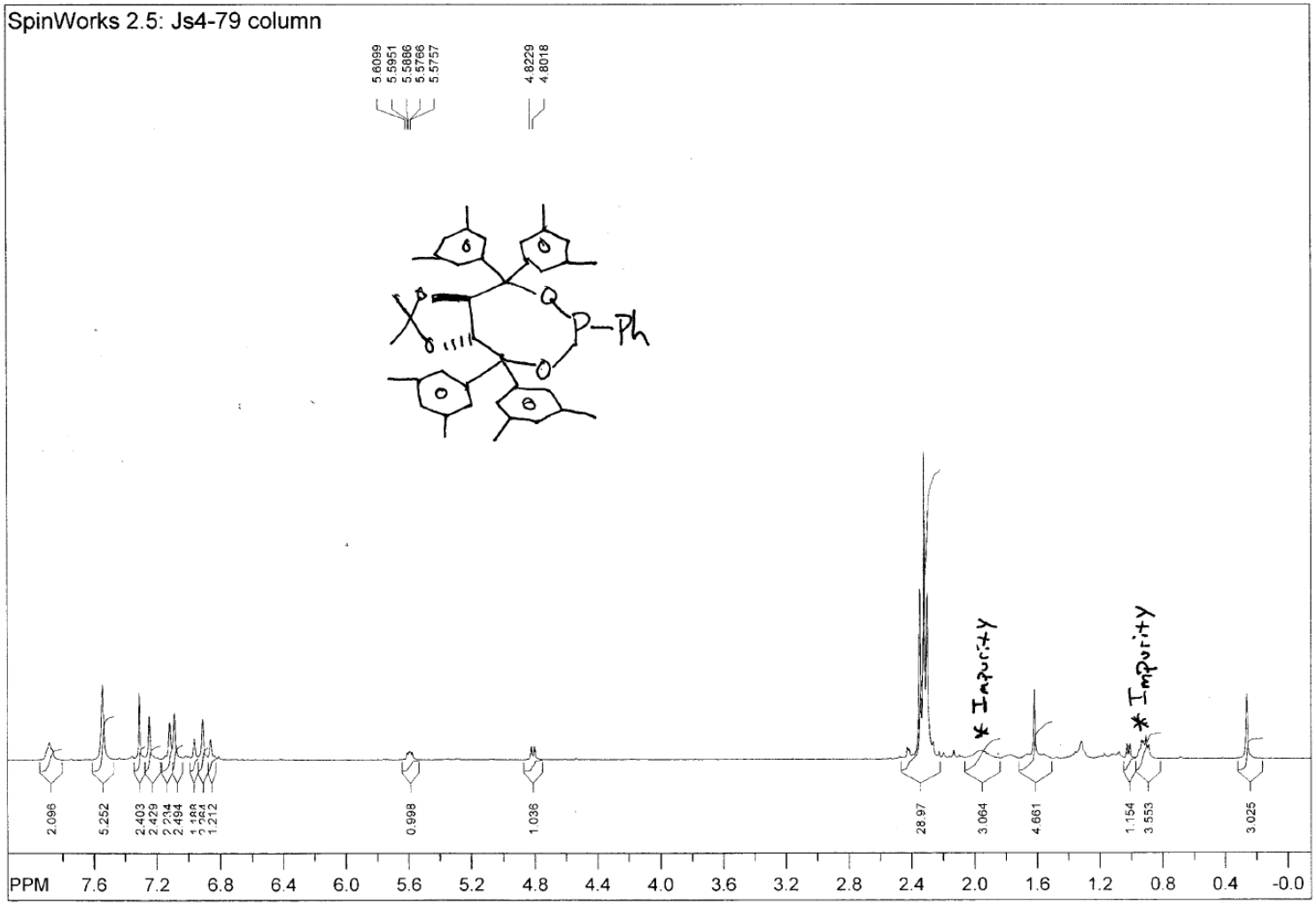
tn C13
at 3.000
np 200168
sw 33361.1
fb 18000
bs 4
tpwr 54
pw 7.0
d1 2.000
tof 818.6
nt 1600
ct 944
alock n
gain not used
FLAGS
i1 n
in n
dp y
hs nn
DISPLAY
sp -228.0
wp 25601.4
vs 132
sc 0
wc 250
hzmm 102.41
is 500.00
rfl 13631.1
rfp 9676.6
th 4
ins 100.000
nm cdc ph
DEC. & VT
dfrq 499.784
dn H1
dpwr 39
dof 0
dm yyy
dmm w
dmf 11905
dseq 1.0
dres n
homo PROCESSING
lb 1.00
wtfile
prgc ft
fn not used
math f
werr
wexp
wbs
wnt
wft
dfrq2
dof2
dm2
dmm2
dmf2
dseq2
dres2
homo2
149.752
149.520
148.884
148.782
146.311
145.554
142.496
141.556
140.565
130.499
130.119
129.918
128.176
128.116
123.826
122.252
121.626
120.711
120.429
120.301
120.209
110.001
84.388
84.356
84.237
84.178
84.093
83.937
83.171
83.129
77.253
77.000
76.745
35.021
34.881
34.765
34.753
31.527
31.482
31.454
31.405
28.092
23.679
ppm



[3,5-(Me)$_2$TADDOL]PPh (2.116). Prepared in 62% yield according to the procedure used to synthesize **2.114** on page 223. A white solid. Mp 116-130 ^{o}C (sealed capillary, decomp.). R_f = 0.35 (SiO_2, 15:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 2991 (m), 2920 (s), 2865 (m), 1776 (w), 1599 (s), 1463 (s), 1379 (m), 1252 (m), 1214 (s), 1155 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.85-7.94 (2H, m), 7.54 (5H, s), 7.31 (2H, s), 7.12 (2H, s), 7.09 (2H, s), 6.96 (1H, s), 6.91 (2H, s), 6.86 (1H, s), 5.59 (1H, dd, *J* = 8.5 Hz, *J* = 5.5 Hz), 4.81 (1H, d, *J* = 8.5 Hz), 2.35 (6H, s), 2.32 (12H, s), 2.30 (6H, s), 1.62 (3H, s) 0.26 (3H, s); ^{13}C NMR ($CDCl_3$): δ 146.7, 146.1, 141.6, 141.3, 137.1, 136.8, 136.7, 136.2, 130.3, 129.9, 129.7, 129.1, 128.9, 128.7, 128.3, 128.2, 127.2, 126.3, 125.3, 125.2, 111.2, 84.14, 83.23, 83.16, 82.79, 82.55, 82.14, 27.97, 25.08, 21.67, 21.55. ^{31}P NMR ($CDCl_3$): δ 155.7. LRMS (ESI+) Calcd for $C_{45}H_{49}O_4P$ $(M + Na)^+$: 707.3, Found $(M + Na)^+$: 706.7. $[\alpha]_D^{20}$ = -80^{o} (*c* = 3.0, $CHCl_3$).



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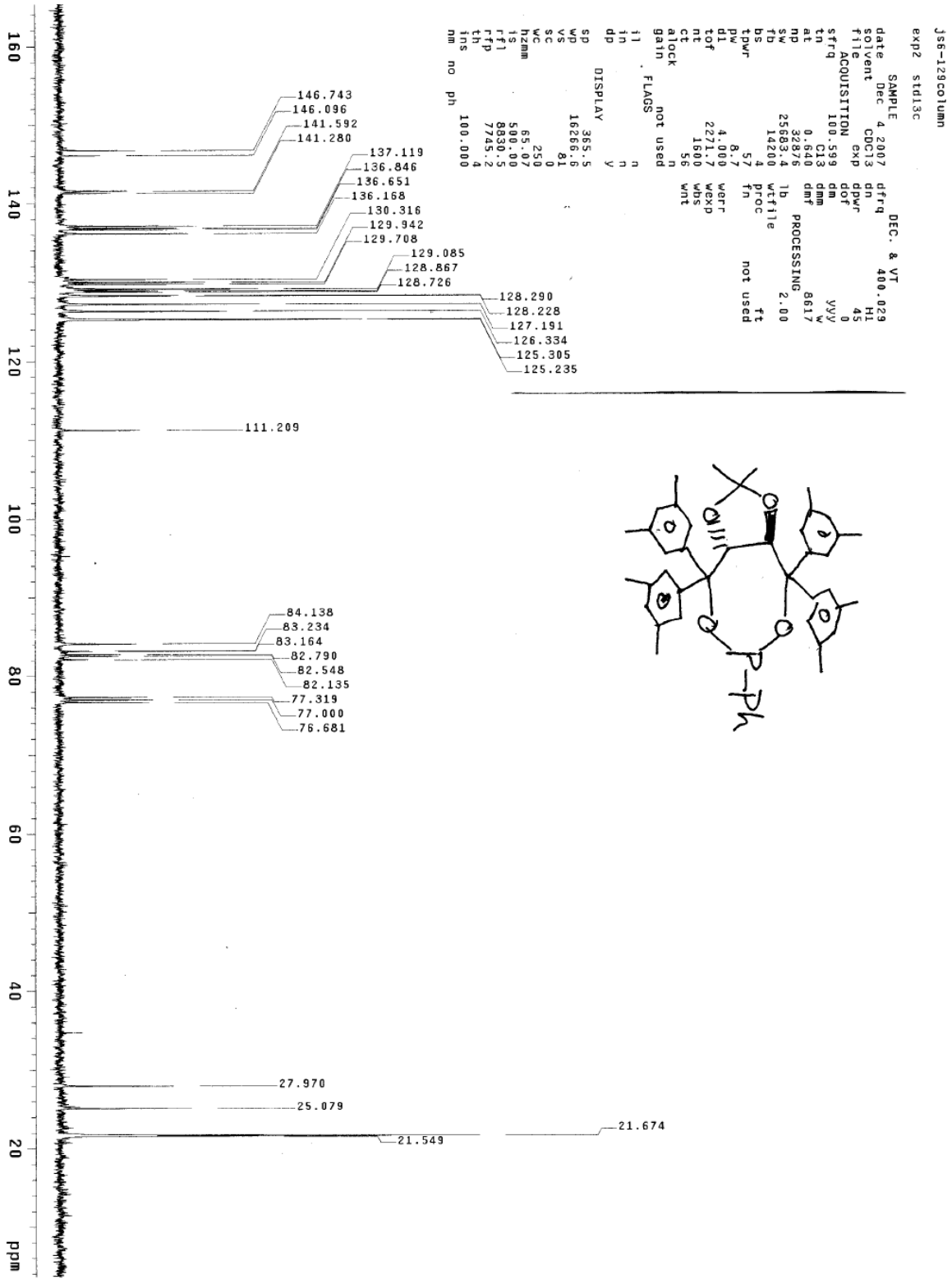
time domain size: 32768 points
width: 6410.26 Hz = 16.023542 ppm = 0.195626 Hz/pt
number of scans: 8

freq. of 0 ppm: 400.049993 MHz
processed size: 32768 complex points
LB: 0.300 GB: 0.0000
Hz/cm: 132.730 ppm/cm: 0.33178


js6-129column
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solvent CDCl3
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sw 25683.4
fb 14200
bs 4
tpwr 57
pw 8.7
d1 4.000
tof 2271.7
nt 1600
ct 56
alock n
gain n
FLAGS
il n
in n
dp y
DISPLAY
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wp 16266.6
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wc 250
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is 500.00
rfl 8830.5
rfp 7745.2
th 4
ins 1
nm no ph
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DEC. & VT
dfrq 400.029
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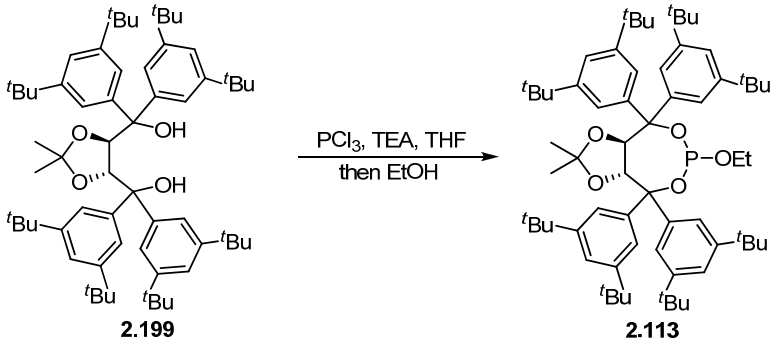
dpwr 45
dof 0
dm yyy
dmm w
dmf 8617
PROCESSING
lb 2.00
wtfile
proc ft
fn not used
not used
146.743
146.096
141.592
141.280
137.119
136.846
136.651
136.168
130.316
129.942
129.708
129.085
128.867
128.726
128.290
128.228
127.191
126.334
125.305
125.235
111.209
84.138
83.234
83.164
82.790
82.548
82.135
77.319
77.000
76.681
27.970
25.079
21.674
21.549
160
140
120
100
80
60
40
20
ppm

Phosphite ligand syntheses:

Synthesis of 2.113

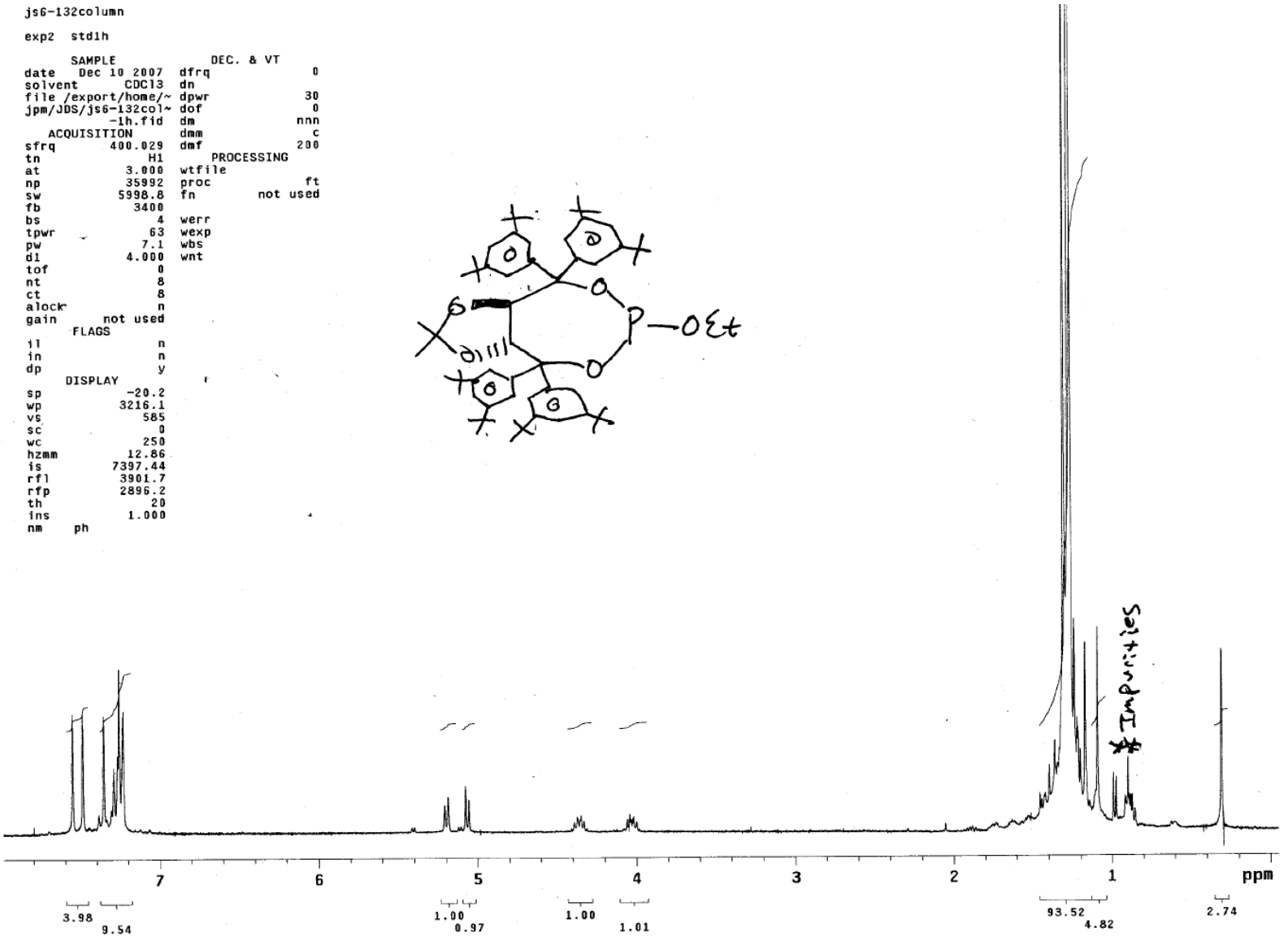


2.199 **2.113**

To 0.179 g (0.195 mmol) of **2.199** in an oven-dried 2-dram vial with stir-bar, under N_2, was added 0.80 mL of THF. The mixture was cooled to 0 ^oC, and 0.092 mL (0.66 mmol) of TEA was added, followed by dropwise addition of 18.7 μL (0.215 mmol) of PCl_3. A white precipitate immediately formed, and the reaction was allowed to warm to room temperature and allowed to stir for 1 h. After cooling to 0 ^oC, 0.080 mL (1.4 mmol) of EtOH was added, and the reaction was allowed to warm to room temperature and allowed to stir for 3 h. The mixture was then diluted with Et_2O and filtered through a pad of celite. Removal of volatile material under reduced pressure, followed by purification using silica gel chromatography (hexanes/EtOAc) afforded 0.154 g (0.156 mmol, 80%) of **2.113** as a white foamy solid.

[3,5-(^{t}Bu)$_2$TADDOL]POEt (2.113). Mp 72-100 ^oC (sealed capillary). R_f = 0.36 (SiO_2, 30:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3075 (w), 2961 (s), 2902 (m), 2868 (m), 1788 (w), 1599 (m), 1476 (m), 1451 (m), 1392 (m), 1358 (m), 1248 (m), 1202 (m), 1168 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55 (2H, s), 7.49 (2H, s), 7.36 (2H, s), 7.21-7.32 (6H,

m), 5.20 (1H, d, *J* = 8.4 Hz), 5.07 (1H, d, *J* = 8.4 Hz), 4.30-4.42 (1H, m), 3.97-4.10 (1H, m), 1.18-1.36 (75H, m), 1.09 (3H, s), 0.31 (3H, s); ^{13}C NMR ($CDCl_3$): δ 149.7, 149.2, 148.9, 148.7, 145.7, 141.3, 140.9, 123.6, 123.3, 123.0 121.6, 121.4, 120.7, 120.3, 120.2, 120.1, 110.9, 84.21, 83.50, 83.27, 83.13, 82.51, 58.59, 34.92, 34.87, 34.83, 31.53, 31.27, 27.18, 25.17, 22.71, 17.10, 14.15. ^{31}P NMR ($CDCl_3$): δ 133.5. LRMS (ESI+) Calcd for $C_{65}H_{97}O_5P$ $(M + Na)^+$: 1011.7, Found $(M + Na)^+$: 1011.3. $[\alpha]_D^{20}$ = -68° (*c* = 3.0, $CHCl_3$).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date Dec 10 2007
solvent CDCl3
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ct 8
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in n
dp y
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vs 585
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is 7397.44
rfl 3901.7
rfp 2896.2
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ins 1.000
nm ph
DEC. & VT
dfrq 0
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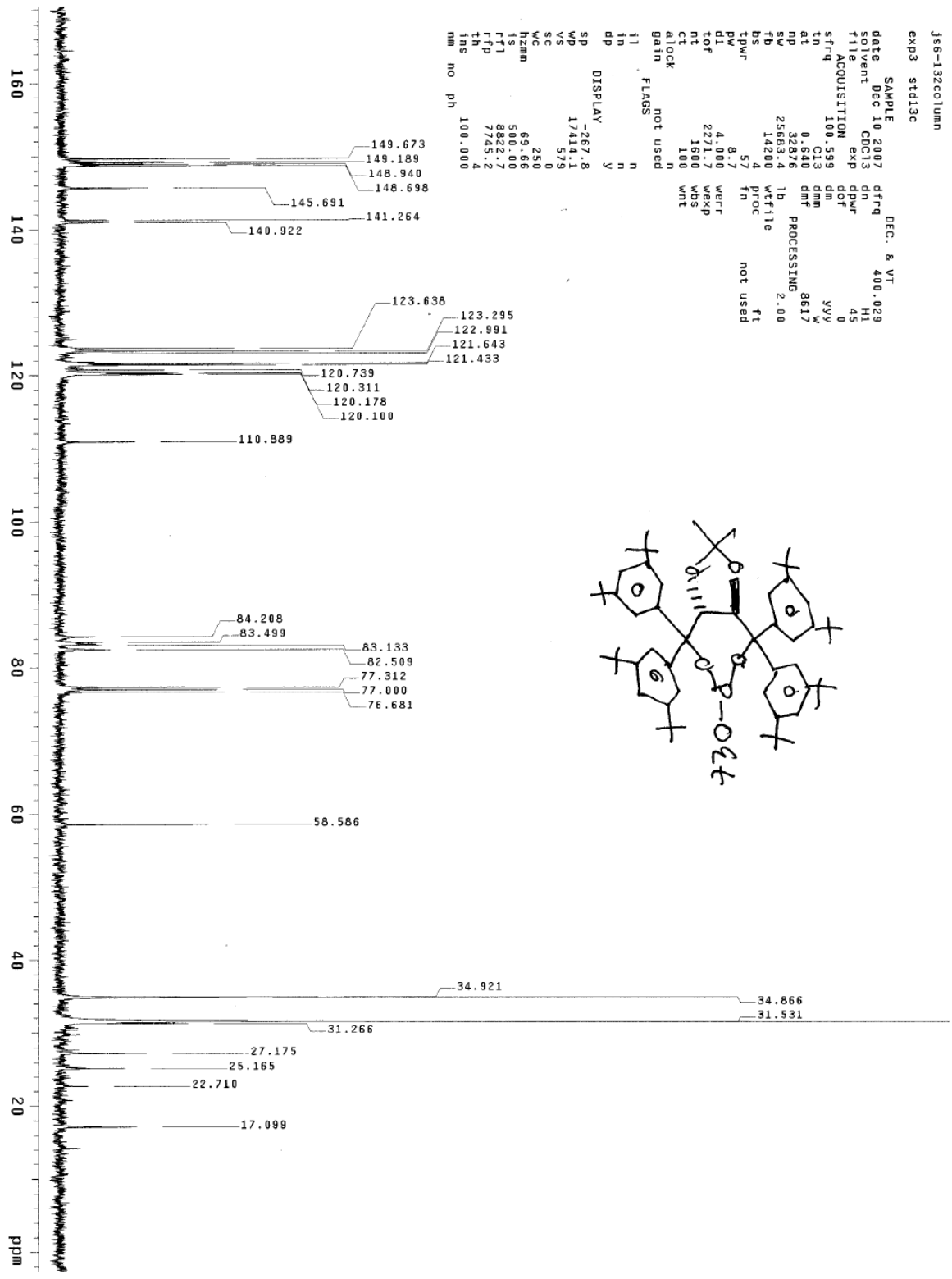
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
P-OEt
* Impurities
7
6
5
4
3
2
1
ppm
3.98
9.54
1.00
0.97
1.00
1.01
93.52
4.82
2.74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date Dec 10 2007
solvent CDCl3
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at 0.640
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sw 25683.4
fb 14200
bs 4
tpwr 57
pw 8.7
d1 4.000
tof 2271.7
nt 100
ct 1600
alock n
gain n
FLAGS
il n
in n
dp y
DISPLAY
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vs 579
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wc 250
hzmm 69.66
is 500.00
rfl 8822.7
rfp 7745.2
th 4
ins 1
nm no ph
100.000
DEC. & VT
dfrq 400.029
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wtfile
proc ft
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120.100
110.889
84.208
83.499
83.133
82.509
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76.681
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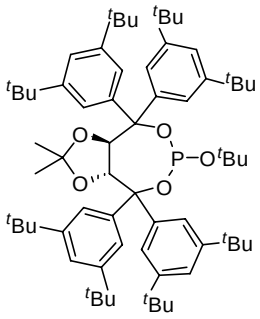
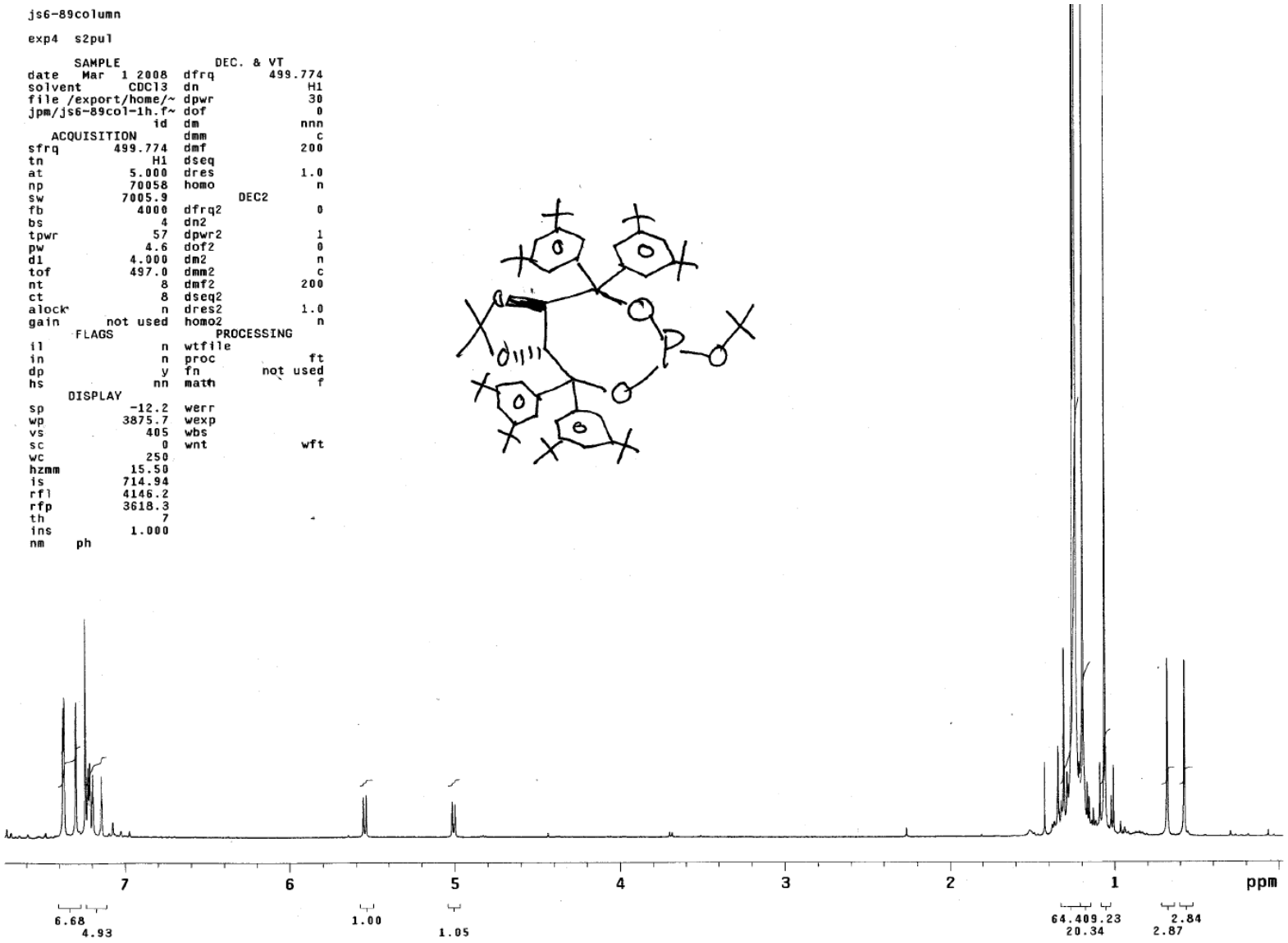
20
ppm



[3,5-(^{t}Bu)$_2$TADDOL]PO^{t}Bu (2.167). Prepared in 19% (48% brsm) yield according to the procedure used to synthesize **2.113** on page 230. A white solid. R_f = 0.38 (SiO_2, 30:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3080 (w), 2958 (s), 2906 (s), 2861 (s), 1771 (w), 1687 (w), 1603 (s), 1476 (s), 1451 (m), 1392 (m), 1248 (s), 1206 (s), 1168 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.38 (2H, d, *J* = 1.5 Hz), 7.37 (2H, d, *J* = 2.0 Hz), 7.30 (2H, d, *J* = 2.0 Hz), 7.24 (2H, s), 7.23 (1H, t, *J* = 2.0 Hz), 6.22 (1H, t, *J* = 1.5 Hz), 7.20 (1H, t, *J* = 1.5 Hz), 7.14 (1H, t, *J* = 2.0 Hz), 5.54 (1H, d, *J* = 8.5 Hz), 5.00 (1H, d, *J* = 8.5 Hz), 1.26 (18H, s), 1.25 (18H, s), 1.24 (18H, s), 1.06 (9H, s), 0.68 (3H, s) 0.58 (3H, s); ^{13}C NMR ($CDCl_3$): δ 149.1, 149.0, 148.6, 148.5, 146.4, 142.0, 141.9, 123.8, 123.5, 122.5, 122.3, 121.9, 121.6, 120.4, 120.04, 120.00, 119.9, 110.8, 85.08, 85.02, 84.06, 84.03, 83.36, 83.26, 81.26, 81.22, 77.88, 77.85, 34.82, 34.80, 34.77, 34.73, 31.52, 31.46, 30.68, 30.62, 30.31, 26.19, 26.08. ^{31}P NMR ($CDCl_3$): δ 133.9. $[\alpha]_D^{20}$ = -63^o (*c* = 2.0, $CHCl_3$).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dmf 200
dseq
dres 1.0
homo n
DEC2
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dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
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math f
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wexp
wbs
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6
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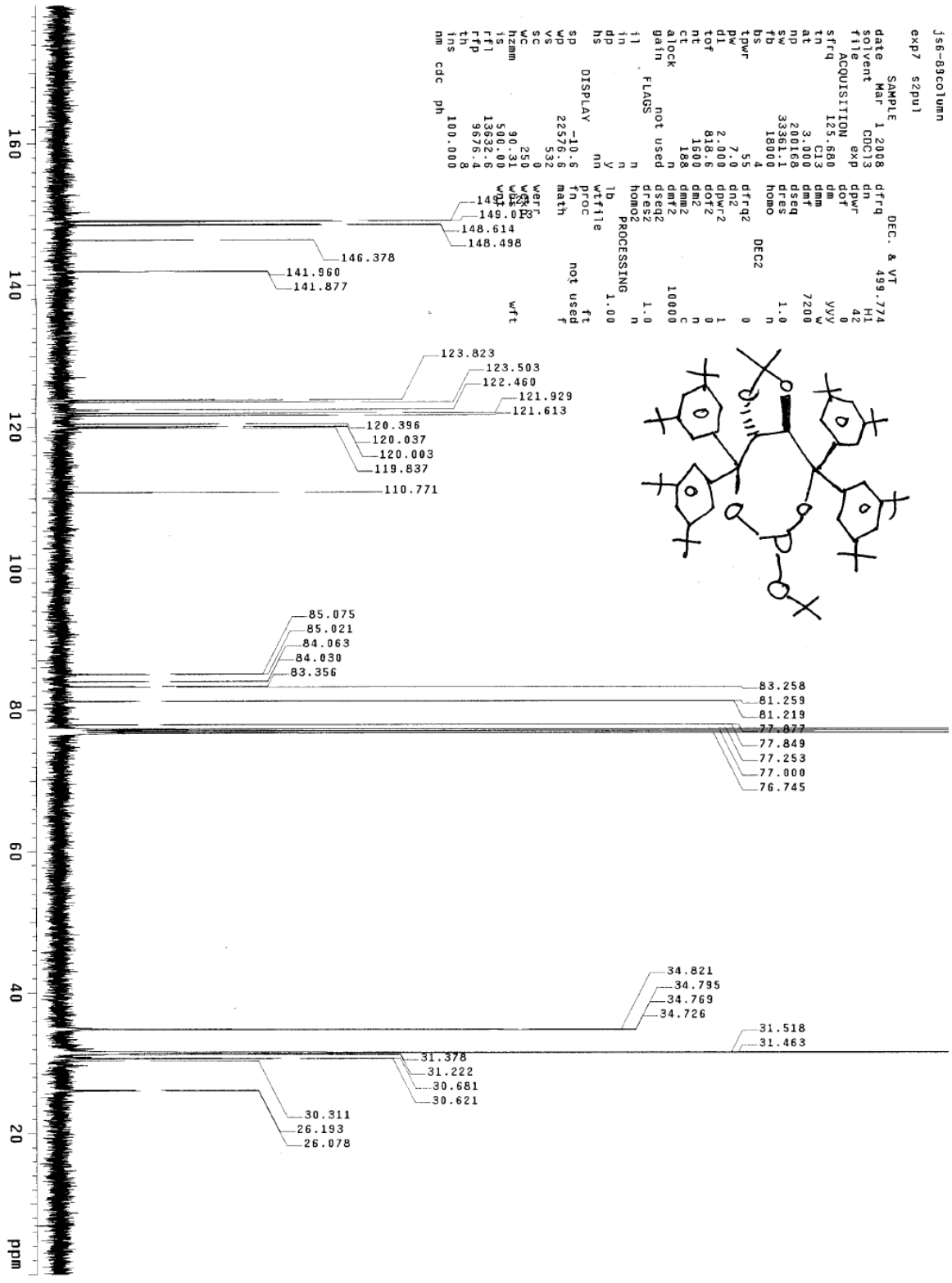
2.84
2.87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date Mar 1 2008
solvent CDCl3
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hs nn
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ph
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dres 1.0
homo n
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dfrq2
dn2
dpwr2
dof2
dm2
dmm2
dmf2
dseq2
dres2
homo2
PROCESSING
lb 1.00
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proc ft
fn not used
math f
wexp
wbs
wnt
wft
wft
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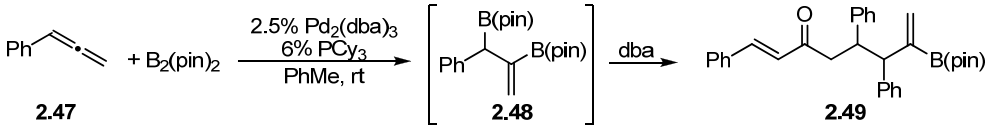
ppm

4. Allylation Procedures

Synthesis of 2.49



An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 4.9 mg (0.0054 mmol) of tris(dibenzylideneacetone)dipalladium(0), 3.6 mg (0.013 mmol) of tricyclohexylphosphine, and 0.43 mL of toluene in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min; then, 65.5 mg (0.258 mmol) of bis(pinacolato)diboron [$B_2(pin)_2$] was added, followed by 25.0 mg (0.215 mmol) of phenyl allene (**2.47**). The vial was capped and allowed to stir at ambient temperature for 4 h. Next, 0.57 mL of toluene was added, followed by 41.5 mg (0.177 mmol) of dba. This mixture was allowed to stir overnight, and water was then added. The mixture was extracted with CH_2Cl_2, and the combined organic layers dried with anhydrous Na_2SO_4. Volatile material was removed under reduced pressure. Silica gel chromatography of the mixture (hexanes/EtOAc) afforded 73.1 mg (0.153 mmol, 79%) of **2.49** as an off-white solid.

(*E*)-1,5,6-Triphenyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octa-1,7-dien-3-one (2.49). R_f = 0.15 (10:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3064 (m), 3028 (m), 2979 (s), 2921 (s), 2860 (m), 1955 (w), 1881 (w), 1811 (w), 1686 (s), 1665 (s), 1607 (s), 1577 (m), 1494 (s), 1451 (s), 1305 (s), 1281 (m), 1141 (s) cm^{-1}; ^1H NMR: δ 7.50 (2H, d, J = 7.6 Hz), 7.13-7.42 (13H, m), 7.08 (1H, t, J = 6.8 Hz), 6.37 (1H, d, J = 16 Hz), 5.59

(1H, d, J = 3.2 Hz), 5.55 (1H, d, J = 3.2), 4.23 (1H, dt, J = 11 Hz, J = 3.2 Hz), 3.82 (1H, d, J = 11 Hz), 2.85 (1H, dd, J = 16 Hz, J = 11 Hz), 2.71 (1H, dd, J = 16 Hz, J = 3.2 Hz), 1.15 (6H, s), 1.13 (6H, s); ^{13}C NMR: δ 199.3, 143.5, 143.3, 141.9, 134.6, 130.8, 130.1, 128.8, 128.73, 128.65, 128.5, 128.1, 128.0, 126.5, 126.4, 126.1, 83.30, 58.29, 47.06, 44.27, 24.81, 24.49. LRMS (ESI+) Calcd for $C_{32}H_{35}BO_3$ $(M + H)^+$: 479.3, Found $(M + H)^+$: 479.3.

js6-170column

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ACQUISITION		dmm	c
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at	3.000	wtfile	
np	35992	proc	ft
sw	5998.8	fn	not used
fb	3400		
bs	4	werr	
tpwr	63	wexp	
pw	7.1	wbs	
d1	4.000	wnt	
tof	0		
nt	16		
ct	8		
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
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wp	3089.9		
vs	57		
sc	0		
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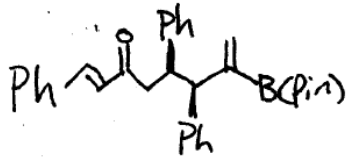
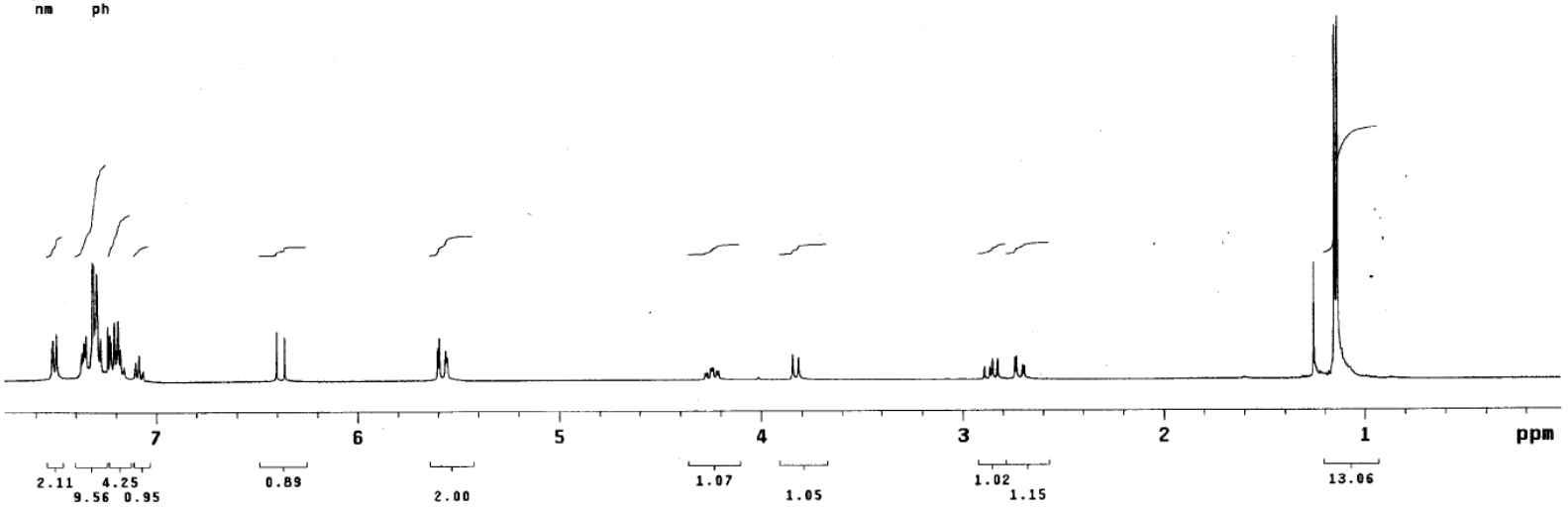
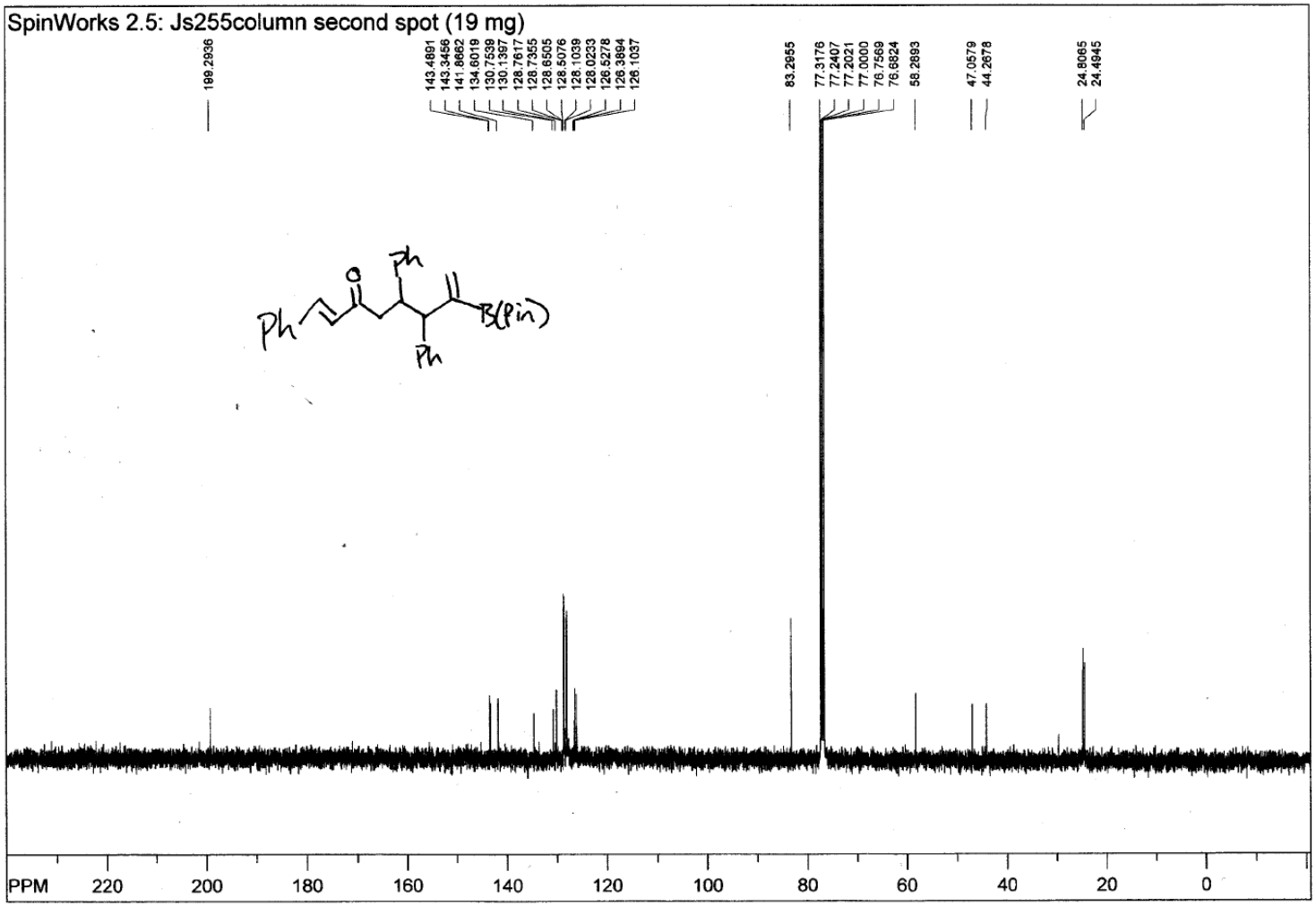
rfl	3902.4		
rfp	2896.2		
th	20		
ins	1.000		
nm	ph		







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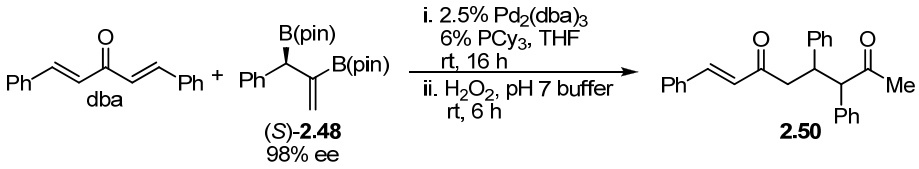
time domain size: 65536 points
width: 26246.72 Hz = 260.840081 ppm = 0.400493 Hz/pt
number of scans: 314

freq. of 0 ppm: 100.612770 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000
Hz/cm: 1049.869 ppm/cm: 10.43360

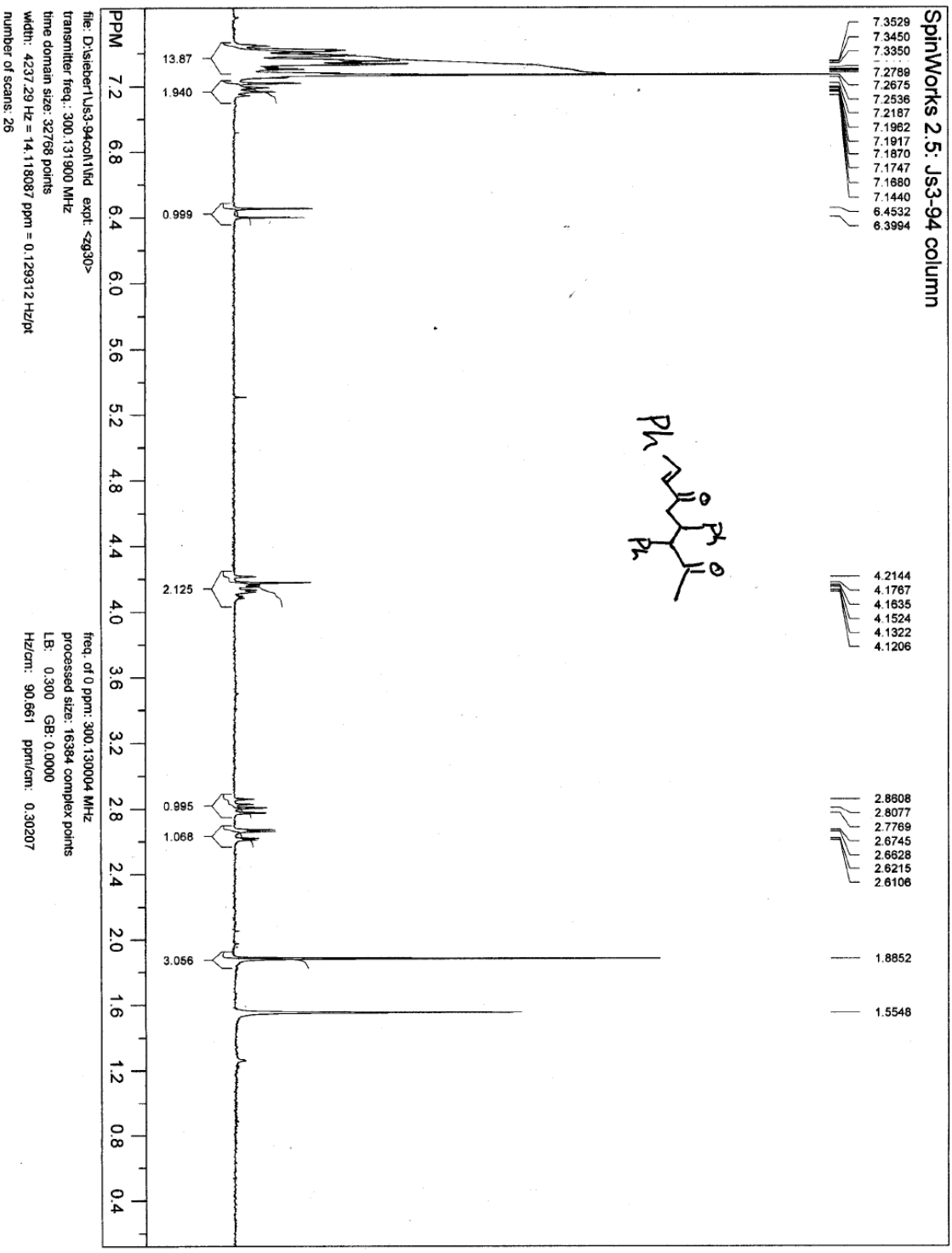
Synthesis of 2.50



An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 1.6 mg (0.0017 mmol) of tris(dibenzylideneacetone)dipalladium(0), 1.1 mg (0.0041 mmol) of tricyclohexylphosphine, and 0.13 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 0.13 mL of THF, 0.15 mL (0.075 mmol) of a 0.50 M stock solution of (*S*)-**2.48** in THF, and 0.10 mL (0.068 mmol) of a 0.68 M stock solution of dba in THF were added sequentially. This mixture was allowed to stir at ambient temperature for 16 h, and then, 0.29 mL of pH 7 buffer and 0.12 mL of aqueous 30% H_2O_2 were added. After stirring this mixture for 6 h, the reaction was quenched by slow addition of saturated aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. Purification using silica gel chromatography (hexanes/EtOAc) afforded 23.4 mg (0.0635 mmol, 93%) of **2.50** as a white solid.

(*E*)-3,4,8-Triphenyloct-7-ene-2,6-dione (2.50). Mp = 176-183 ^{o}C R_f = 0.22 (4:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3063 (m), 3025 (m), 2928 (m), 1953 (w), 1894 (w), 1805 (w), 1712 (s), 1645 (s), 1607 (s), 1497 (s), 1451 (s), 1421 (m), 1354 (s), 1253 (s) cm^{-1}; ^{1}H NMR: δ 7.10-7.45 (16H, m), 6.42 (1H, d, J = 16 Hz), 4.10-4.25 (2H, m),

2.81 (1H, dd, J = 16 Hz, J = 10 Hz), 2.64 (1H, dd, J = 16 Hz, J = 3.4 Hz), 1.89 (3H, s); ^{13}C NMR: δ 206.6, 198.1, 142.2, 142.1, 136.4, 134.4, 130.2, 129.1, 129.0, 128.8, 128.4, 128.13, 128.10, 127.9, 126.7, 126.0, 64.87, 45.24, 43.71, 30.27. LRMS (ESI+) Calcd for $C_{26}H_{24}O_2$ $(M + H)^+$: 369.2, Found $(M + H)^+$: 369.2.


SpinWorks 2.5: Js3-94 column
7.3529
7.3450
7.3350
7.2789
7.2675
7.2536
7.2187
7.1962
7.1917
7.1870
7.1747
7.1680
7.1440
6.4532
6.3994
4.2144
4.1767
4.1635
4.1524
4.1322
4.1206
2.8808
2.8077
2.7769
2.6745
2.6628
2.6215
2.6106
1.8852
1.5548
13.87
1.940
0.999
2.125
0.995
1.068
3.056
PPM 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4
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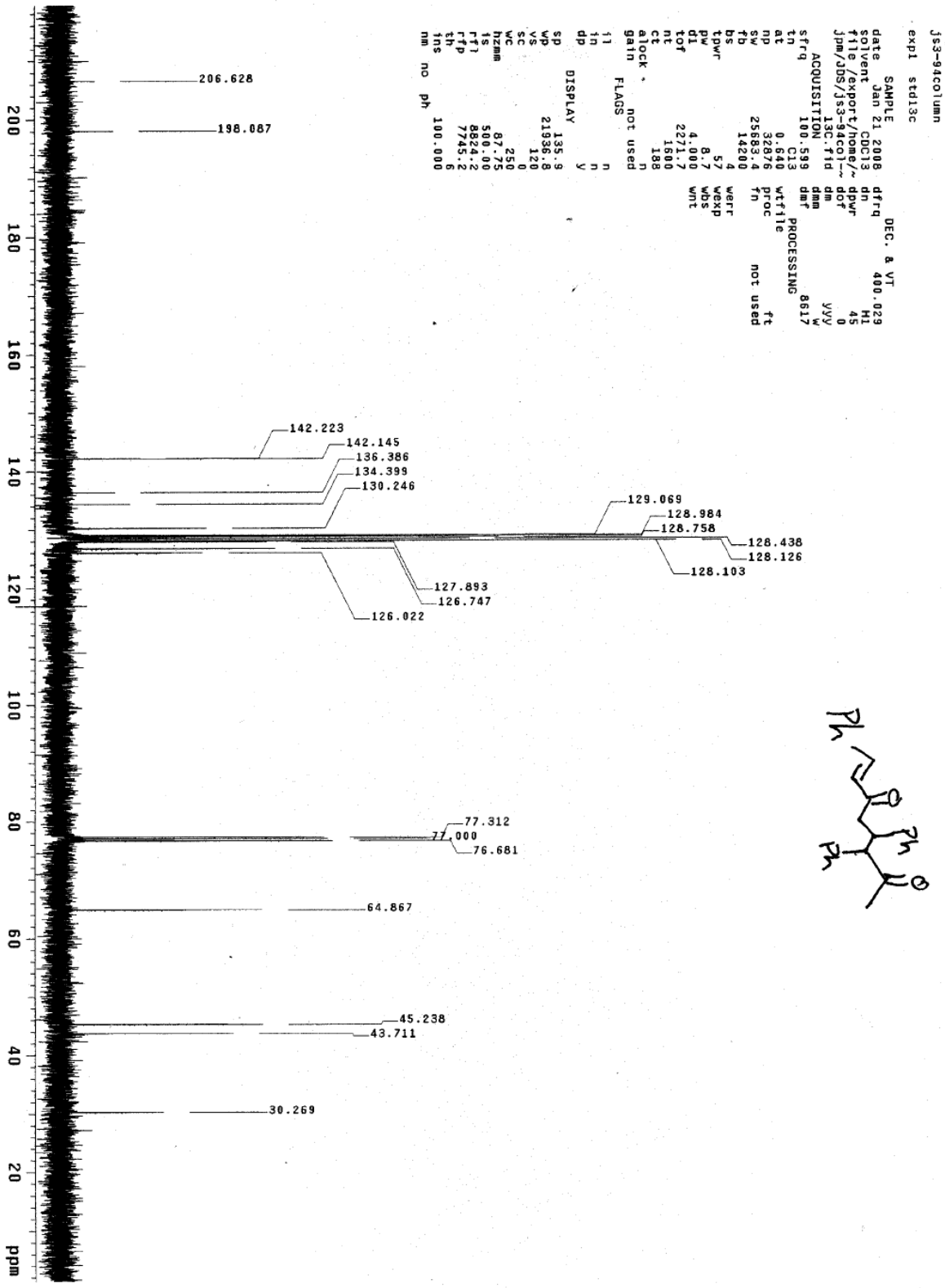
transmitter freq.: 300.131900 MHz
time domain size: 32768 points
width: 4237.29 Hz = 14.118087 ppm = 0.129312 Hz/pt
number of scans: 26
freq. of 0 ppm: 300.130004 MHz
processed size: 16384 complex points
LB: 0.300 GB: 0.0000
Hz/cm: 90.661 ppm/cm: 0.30207


206.628
198.087
142.223
142.145
136.386
134.399
130.246
129.069
128.984
128.758
128.438
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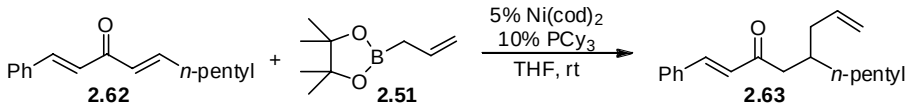
128.103
127.893
126.747
126.022
77.312
77.000
76.681
64.867
45.238
43.711
30.269
200
180
160
140
120
100
80
60
40
20
ppm

General procedure for the non-enantioselective conjugate allylation (Table 2.3):

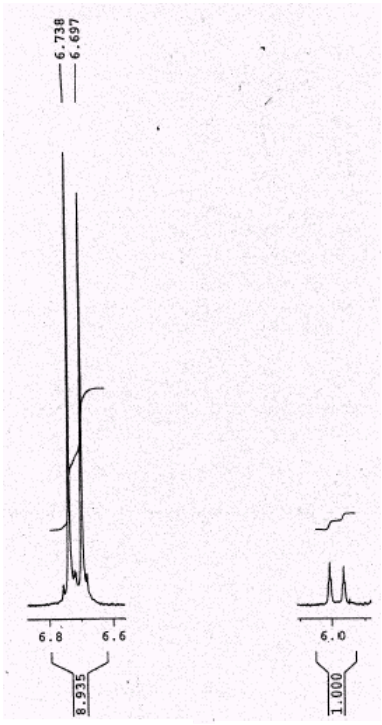


An oven-dried 20 mL scintillation vial, equipped with a magnetic stir-bar, was charged with 6.0 mg (0.022 mmol) of bis(1,5-cyclooctadiene)nickel, 12.3 mg (0.0438 mmol) of tricyclohexylphosphine, and 1.46 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 44.2 mg (0.263 mmol) of **2.51** was added followed by 50.0 mg (0.219 mmol) of **2.62**. The vial was capped, sealed with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for the time period given in Table 2.3 (page 120). After this time period, ~15 mL of water was added, and the mixture transferred to a separatory funnel with CH_2Cl_2. After gently swirling the layers, the organic layer was collected, and the aqueous layer washed with CH_2Cl_2 (1x). The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. NMR analysis of the unpurified mixture was used to determine the chemoselectivity of the reaction. Purification of the mixture using silica gel chromatography (hexanes/EtOAc) afforded 50.7 mg (0.187 mmol, 86%) of **2.63** contaminated with a small amount of the minor constitutional isomer formed from benzylidene conjugate allylation.

(*E*)-5-Allyl-1-phenyldec-1-en-3-one (2.63). The minor constitutional isomer could be removed using iterative chromatography. An oil. R_f = 0.22 (18:1 hexanes:EtOAc); IR (neat): 3064 (w), 2948 (s), 2917 (s), 2858 (s), 1942 (w), 1821 (w), 1689 (s), 1654 (s),

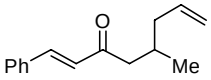
1608 (s), 1445 (s), 1320 (m), 1167 (m) cm^{-1}; ^{1}H NMR: δ 7.48-7.59 (3H, m), 7.37 (3H, m), 6.72 (1H, d, *J* = 16 Hz), 5.76 (1H, m), 5.01 (2H, d, *J* = 12 Hz), 2.61 (1H, dd, *J* = 16 Hz, *J* = 6.0 Hz), 2.52 (1H, dd, *J* = 16 Hz, *J* = 6.0 Hz), 1.95-2.20 (3H, m), 1.15-1.40 (8H, m), 0.86 (3H, t, *J* = 7.2 Hz); ^{13}C NMR: δ 200.4, 142.2, 136.6, 134.6, 130.3, 128.9, 128.2, 126.6, 116.6, 45.23, 38.26, 34.07, 33.80, 31.97, 26.40, 22.58, 14.03. LRMS (ESI+) Calcd for $C_{19}H_{26}O$ $(M + Na)^{+}$: 293.2, Found $(M + Na)^{+}$: 293.2.

^{1}H NMR analysis of unpurified reaction mixture (400 MHz, $CDCl_3$):



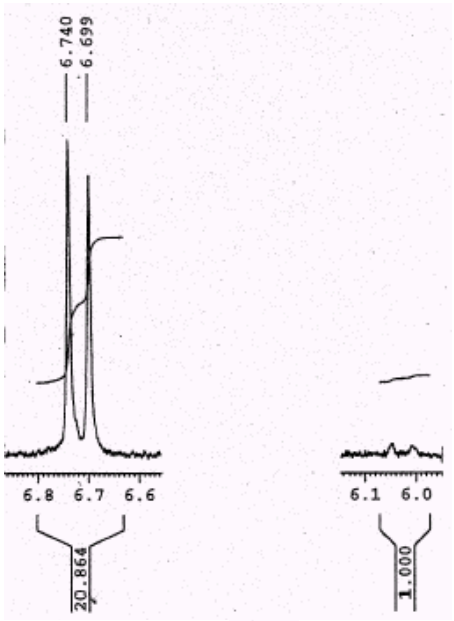
Vinyl CH (minor + major isomers)

Vinyl CH (minor isomer)

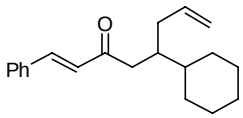


(*E*)-5-Methyl-1-phenylocta-1,7-dien-3-one (2.202). Prepared according to the general procedure used to synthesize **2.63** on page 245. The minor constitutional isomer was not observed in the ^{1}H NMR spectrum of the unpurified reaction mixture. An oil. R_f = 0.24 (12:1 hexanes:EtOAc); IR (neat): 3064 (m), 2955 (s), 2917 (s), 1946 (w), 1829 (w), 1689 (s), 1666 (s), 1611 (s), 1452 (s), 1324 (s), 1173 (s) cm^{-1}; ^{1}H NMR: δ 7.45-7.57 (3H, m), 7.28-7.44 (3H, m), 6.72 (1H, d, *J* = 16 Hz), 5.77 (1H, m), 5.02 (2H, d, *J* = 14 Hz), 2.66 (1H, dd, *J* = 16 Hz, *J* = 6.0 Hz), 2.43 (1H, dd, *J* = 16 Hz, *J* = 8.0 Hz), 2.19 (1H, m), 1.95-2.12 (2H, m), 0.95 (3H, d, *J* = 6.4 Hz); ^{13}C NMR: δ 200.2, 142.4, 136.7, 134.5, 130.4, 128.9, 128.2, 126.5, 116.5, 47.43, 41.20, 29.52, 19.77. LRMS (ESI+) Calcd for $C_{15}H_{18}O$ (M + Na)$^{+}$: 237.1, Found (M + Na)$^{+}$: 237.1.

^{1}H NMR analysis of unpurified reaction mixture (400 MHz, $CDCl_3$):

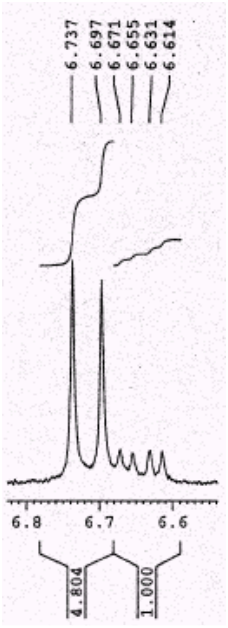


Vinyl CH (minor + major) Vinyl CH (minor isomer)

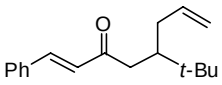


(*E*)-5-Cyclohexyl-1-phenylocta-1,7-dien-3-one (2.203). Prepared according to the general procedure used to synthesize **2.63** on page 245. Isolated as an inseparable mixture of constitutional isomers. An oil. R_f = 0.29 (12:1 hexanes:EtOAc); IR (neat): 3056 (m), 2913 (s), 2842 (s), 1953 (w), 1817 (w), 1685 (s), 1662 (s), 1603 (s), 1441 (s), 1320 (m), 1181 (m) cm^{-1}; ^1H NMR: δ 7.52 (3H, m, major), 7.37 (3H, m, major), 7.25 (2H, m, minor), 7.16 (3H, m, minor), 6.72 (1H, d, *J* = 16 Hz, major), 6.65 (1H, dd, *J* = 16 Hz, *J* = 6.8 Hz, minor), 5.93 (1H, d, *J* = 16 Hz, minor), 5.74 (1H, m, major), 5.63 (1H, m, minor), 4.90-5.05 (4H, m, major & minor), 3.28 (1H, p, *J* = 7.2 Hz, minor), 2.81 (2H, m, minor), 2.61 (1H, dd, *J* = 16 Hz, *J* = 6.0 Hz, major) 2.52 (1H, dd, *J* = 16 Hz, *J* = 6.8 Hz, major), 2.37 (2H, t, *J* = 7.2 Hz, minor), 2.16 (1H, m, major), 1.91-2.10 (3H, m, major & minor), 1.57-1.78 (10H, m, major & minor), 1.36 (1H, m, major), 0.94-1.29 (10H, m, major & minor); ^{13}C NMR: δ 200.6, 199.7, 152.5, 144.2, 142.1, 137.4, 136.2, 134.6, 130.3, 128.9, 128.3, 128.2, 128.1, 127.5, 126.5, 126.3, 116.6, 116.3, 50.06, 42.50, 41.00, 40.56, 40.52, 40.33, 39.16, 35.85, 31.67, 30.00, 29.63, 26.66, 25.86, 25.64. LRMS (ESI+) Calcd for $C_{20}H_{26}O$ $(M + Na)^+$: 305.2, Found $(M + Na)^+$: 305.2.

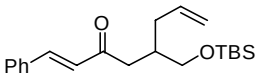
^{1}H NMR analysis of unpurified reaction mixture (400 MHz, $CDCl_3$):



Vinyl CH
(minor + major isomers)

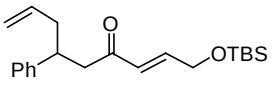


(*E*)-5-*t*-Butyl-1-phenylocta-1,7-dien-3-one (2.204). Prepared according to the general procedure used to synthesize **2.63** on page 245. The minor constitutional isomer was not observed in the ^{1}H NMR spectrum of the unpurified reaction mixture. An oil. R_f = 0.24 (15:1 hexanes:EtOAc); IR (neat): 3064 (m), 2959 (s), 2870 (m), 1953 (w), 1814 (w), 1689 (s), 1654 (s), 1608 (s), 1445 (s), 1363 (s), 1185 (m) cm^{-1}; ^{1}H NMR: δ 7.48-7.57 (3H, m), 7.37 (3H, m), 6.73 (1H, d, *J* = 16 Hz), 5.72 (1H, m), 4.97 (1H, d, *J* = 17 Hz), 4.91 (1H, d, *J* = 10 Hz) 2.66 (1H, dd, *J* = 17 Hz, *J* = 4.0 Hz), 2.46 (1H, dd, *J* = 17 Hz, *J* = 6.0 Hz), 2.32-2.41 (1H, m), 2.13 (1H, m), 1.78 (1H, m), 0.89 (9H, s); ^{13}C NMR: δ 200.1, 141.6, 138.4, 134.5, 130.1, 128.7, 128.0, 126.3, 115.8, 42.47, 41.99, 35.65, 33.28, 27.50. LRMS (ESI+) Calcd for $C_{18}H_{24}O$ (M + Na)$^{+}$: 279.2, Found (M + Na)$^{+}$: 279.2.



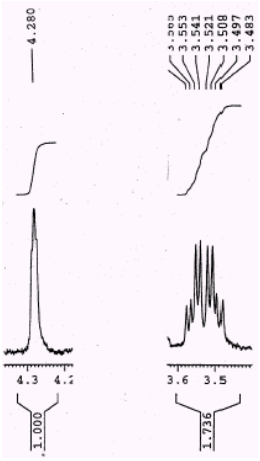
(*E*)-5-[(*t*-Butyldimethylsilyloxy)methyl]-1-phenylocta-1,7-dien-3-one (2.205). Prepared according to the general procedure used to synthesize **2.61** on page 245. Isolated as the major constitutional isomer when **2.70** was used as the substrate in the conjugate allylation. Note that pH 7 buffer was used in the aqueous workup rather than water. Constitutional isomers were separable using column chromatography (SiO_2/hexanes:EtOAc). An oil. R_f = 0.26 (14:1 hexanes:EtOAc); IR (neat): 3076 (m), 2955 (s), 2924 (s), 2854 (s), 1689 (s), 1662 (s), 1611 (s), 1471 (m), 1363 (m), 1251 (s), 1103 (s) cm^{-1}; ^{1}H NMR: δ 7.49-7.59 (3H, m), 7.37 (3H, m), 6.72 (1H, d, *J* = 16 Hz), 5.77 (1H, m), 5.03 (2H, m), 3.56 (1H, dd, *J* = 10 Hz, *J* = 4.8 Hz), 3.51 (1H, dd, *J* = 10 Hz, *J* = 5.6 Hz), 2.77 (1H, dd, *J* = 16 Hz, *J* = 6.8 Hz), 2.53 (1H, dd, *J* =

16 Hz, *J* = 6.0 Hz), 2.11-2.31 (2H, m), 2.07 (1H, m), 0.87 (9H. s), 0.015 (3H, s), 0.0030 (3H, s); ^{13}C NMR: δ 200.2, 142.3, 136.5, 134.6, 130.3, 128.9, 128.2, 126.7, 116.6, 64.73, 41.91, 36.94, 35.63, 25.89, 18.26, -5.46. LRMS (ESI+) Calcd for $C_{21}H_{32}O_2Si$ $(M + Na)^+$: 367.2, Found $(M + Na)^+$: 367.3.

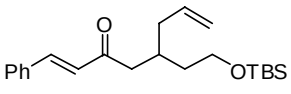


(*E*)-1-(*t*-Butyldimethylsilyloxy)-6-phenylnona-2,8-dien-4-one (2.206). Prepared according to the general procedure used to synthesize **2.63** on page 245. Isolated as the minor constitutional isomer when **2.70** was used as the substrate in the conjugate allylation. Note that pH 7 buffer was used in the aqueous workup rather than water. Constitutional isomers were separable using column chromatography (SiO_2/hexanes:EtOAc). An oil. R_f = 0.18 (14:1 Hexanes:EtOAc); IR (neat): 3056 (m), 3029 (m), 2948 (s), 2924 (s), 2858 (s), 1697 (s), 1670 (s), 1635 (s), 1468 (m), 1359 (m), 1251 (s), 1134 (s) cm^{-1}; ^{1}H NMR: δ 7.20-7.30 (2H, m), 7.10-7.20 (3H, m), 6.76 (1H, dt, *J* = 16 Hz, *J* = 3.2 Hz), 6.28 (1H, d, *J* = 16 Hz), 5.63 (1H, m), 4.96 (1H, d, *J* = 16 Hz), 4.93 (1H, d, *J* = 10 Hz), 4.28 (2H, m), 3.31 (1H, p, *J* = 7.2 Hz), 2.85 (2H, m), 2.37 (2H, t, *J* = 7.2 Hz), 0.90 (9H, s), 0.045 (6H, s); ^{13}C NMR: δ 198.9, 145.3, 144.2, 136.2, 128.4, 127.9, 127.5, 126.3, 116.7, 62.23, 46.70, 40.81, 40.60, 25.84, 18.35, -5.45. LRMS (ESI+) Calcd for $C_{21}H_{32}O_2Si$ $(M + Na)^+$: 367.2, Found $(M + Na)^+$: 367.3.

^{1}H NMR analysis of unpurified reaction mixture (400 MHz, $CDCl_3$):



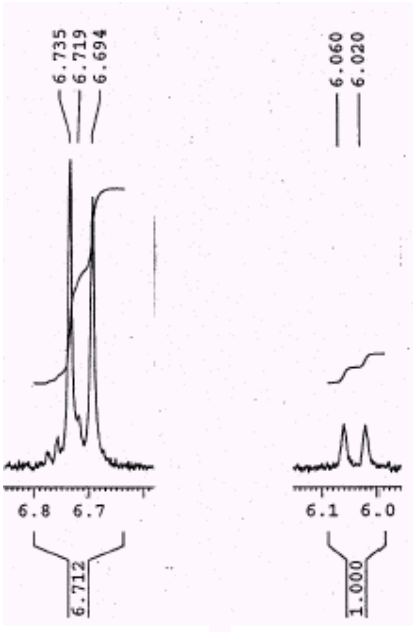
Carbinol (minor isomer) Carbinol (major isomer)



(*E*)-5-[(2-*t*-Butyldimethylsilyloxy)ethyl]-1-phenylocta-1,7-dien-3-one (2.207). Prepared according to the general procedure used to synthesize **2.63** on page 245. Note that pH 7 buffer was used in the aqueous workup rather than water. Constitutional isomers were separable using iterative column chromatography (SiO_2/hexanes:EtOAc). An oil. R_f (major) = 0.25 (15:1 hexanes:EtOAc); R_f (minor) = 0.18 (15:1 hexanes:EtOAc); IR (major, neat): 3068 (m), 2948 (s), 2932 (s), 2847 (s), 1953 (w), 1817 (w), 1682 (s), 1658 (s), 1611 (s), 1468 (m), 1328 (m), 1254 (s) cm^{-1}; ^{1}H NMR: δ (major) 7.45-7.57 (3H, m), 7.37 (3H, m), 6.72 (1H, d, *J* = 16 Hz), 5.76 (1H, m), 5.02 (2H, m), 3.66 (2H, m) 2.63 (2H, d, *J* = 6.4 Hz), 2.27 (1H, heptet, *J* = 6.4 Hz), 2.01-2.20 (2H, m), 1.45-1.67 (2H, m), 0.86 (9H, s), 0.020 (6H, s); δ (minor) 7.21-

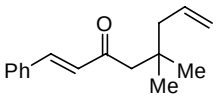
7.30 (2H, m), 7.10-7.20 (3H, m), 6.74 (1H, dt, *J* = 16 Hz, *J* = 7.2 Hz), 6.04 (1H, d, *J* = 16 Hz), 5.62 (1H, m), 4.96 (1H, d, *J* = 15 Hz), 4.93 (1H, d, *J* = 10 Hz), 3.67 (2H, t, *J* = 6.4 Hz), 3.30 (1H, p, *J* = 7.2 Hz), 2.83 (2H, m), 2.35 (4H, m), 0.87 (9H, s), 0.023 (6H, s); ^{13}C NMR: δ (major) 200.1, 142.3, 136.4, 134.6, 130.3, 128.9, 128.2, 126.5, 116.9, 61.20, 45.29, 38.42, 36.61, 31.23, 25.92, 18.26, -5.34. LRMS (ESI+) Calcd for $C_{22}H_{34}O_2Si$ (M + Na)$^+$: 381.2, Found (M + Na)$^+$: 381.3.

^{1}H NMR analysis of unpurified reaction mixture (400 MHz, $CDCl_3$):

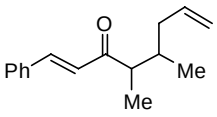


Vinyl CH (minor + major isomers)

Vinyl CH (minor isomer)



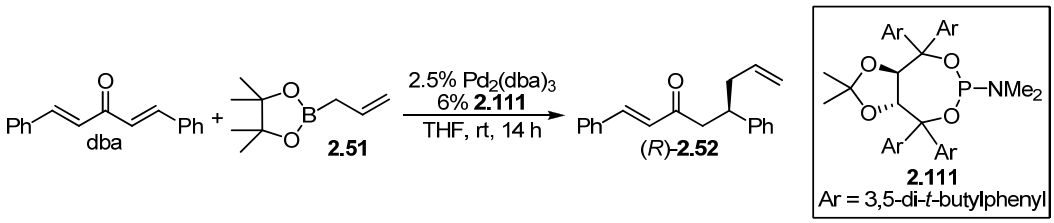
(*E*)-5,5-Dimethyl-1-phenylocta-1,7-dien-3-one (2.208). Prepared according to the general procedure used to synthesize **2.63** on page 245 using 2.0 equiv of **2.51** and 65 ^{o}C reaction temperature. The minor constitutional isomer was not observed in the ^{1}H NMR spectrum of the unpurified reaction mixture. An oil. R_f = 0.26 (14:1 hexanes:EtOAc); IR (neat): 3072 (m), 2959 (s), 2862 (s), 1950 (w), 1814 (w), 1685 (s), 1651 (s), 1608 (s), 1440 (s), 1332 (s), 1200 (s) cm^{-1}; ^{1}H NMR: δ 7.52 (2H, m), 7.49 (1H, d, *J* = 16 Hz), 7.36 (3H, m), 6.72 (1H, d, *J* = 16 Hz), 5.84 (1H, m), 5.05 (2H, m), 2.52 (2H, s), 2.12 (2H, d, *J* = 7.6 Hz), 1.03 (6H, s); ^{13}C NMR: δ 200.0, 141.9, 135.0, 134.6, 130.3, 128.9, 128.3, 127.6, 117.7, 51.49, 46.85, 34.30, 27.40. LRMS (ESI+) Calcd for $C_{16}H_{20}O$ $(M + Na)^+$: 251.1, Found $(M + Na)^+$: 251.2.



(*E*)-4,5-dimethyl-1-phenylocta-1,7-dien-3-one (2.209). Prepared according to the general procedure used to synthesize **2.63** on page 245. Note that the reaction was performed at 65 ^{o}C and quenched with 2.2 equiv of 1.0 M HCl in Et_2O at room temperature before the addition of water. The minor constitutional isomer was not observed in the ^{1}H NMR spectrum of the unpurified reaction mixture. Isolated as an inseparable mixture of diastereomers using column chromatography (SiO_2/hexanes:EtOAc). An oil. R_f = 0.26 (14:1 hexanes:EtOAc); IR (neat): 3076 (m), 2967 (s), 2920 (s), 1942 (w), 1821 (w), 1685 (s), 1651 (s), 1608 (s), 1449 (s), 1324 (s), 1188 (m) cm^{-1}; ^{1}H NMR: δ 7.58 (2H, d, *J* = 16 Hz, major & minor), 7.54 (4H, m, major & minor), 7.37 (6H, major & minor), 6.80 (1H, d, *J* = 16 Hz, major), 6.79 (1H, d, *J* = 16 Hz, minor), 5.76 (2H, m, major & minor), 5.02 (4H, m, major &

minor), 2.80 (1H, p, J = 6.4 Hz, minor), 2.73 (1H, p, J = 6.8 Hz, major), 1.85-2.28 (6H, m, major & minor), 1.13 (3H, d, J = 6.8 Hz, major), 1.06 (3H, d, J = 7.2 Hz, minor), 0.92 (3H, d, J = 6.4 Hz, major), 0.84 (3H, d, J = 6.4 Hz, minor); ^{13}C NMR: δ 203.6, 203.5, 142.3, 136.9, 136.65, 136.59, 134.6, 130.4, 130.3, 128.9, 128.3, 128.27, 125.3, 125.1, 116.5, 116.4, 49.60, 48.47, 39.67, 37.42, 35.31, 34.59, 17.72, 15.25, 13.65, 11.35. LRMS (ESI+) Calcd for $C_{16}H_{20}O$ $(M + Na)^+$: 251.1, Found $(M + Na)^+$: 251.1.

Asymmetric Synthesis of 2.52

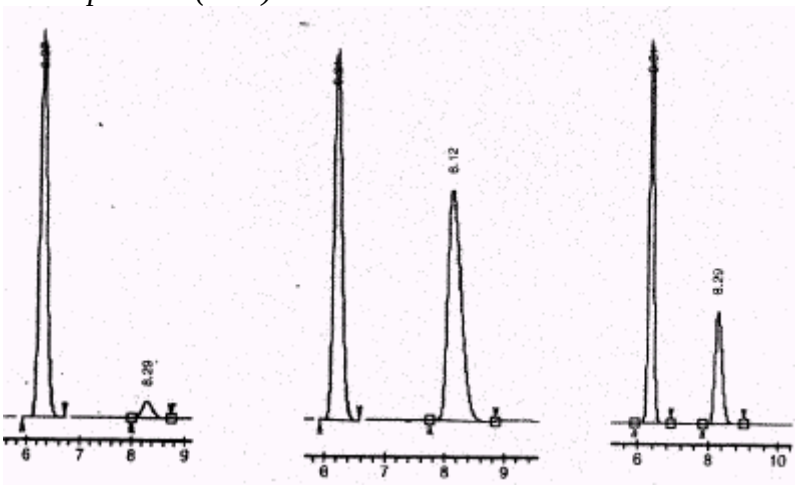


An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 2.5 mg (0.0027 mmol) of tris(dibenzylideneacetone)dipalladium, 6.3 mg (0.0064 mmol) of chiral ligand **2.111**, and 0.71 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 19.8 mg (0.118 mmol) of **2.51** was added followed by 25.0 mg (0.107 mmol) of dba. The vial was capped, sealed with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 24 h. After this time period, water was added, and the mixture transferred to a separatory funnel with CH_2Cl_2. After gently swirling the layers, the organic layer was collected, and the aqueous layer washed with CH_2Cl_2 (2x). The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure.

Silica gel chromatography (hexanes/EtOAc) afforded 26.3 mg (0.0952 mmol, 89%) of (*R*)-**2.52**. Spectral data were consistent with the literature.[1]

Proof of stereochemistry. Stereochemical ratios were determined by comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction when using $Ni(cod)_2$ as the precatalyst. Absolute stereochemistry was determined by subjecting the conjugate allylation product to ring closing metathesis conditions using the Hoveyda-Grubbs' second generation catalyst, in CH_2Cl_2, to afford 5-phenyl-2-cycohexen-1-one (see page 358). The optical rotation was measured ($[\alpha]_D^{20}$ = +40° (*c* = 0.5, $CHCl_3$)) and compared to the known literature value.[2]

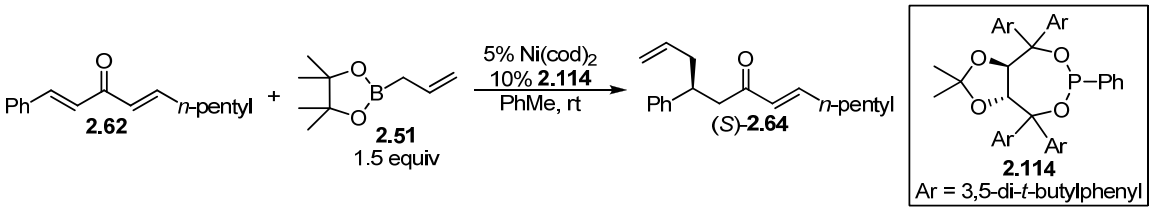
*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 3 mL/min, 4% MeOH) analysis of conjugate allylation product (**2.52**):*



Allylation product | Racemic | Allylation product + racemic coinjection

[1] Mandal, S. K.; Amin, Sk. R.; Crowe, W. E.; *J. Am. Chem. Soc.* **2001**, *123*, 6457.
[2] Hareau, G. P-J.; Koiwa, M.; Hikichi, S; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640.

General procedure for the asymmetric Ni-catalyzed conjugate allylation (Table 2.7):



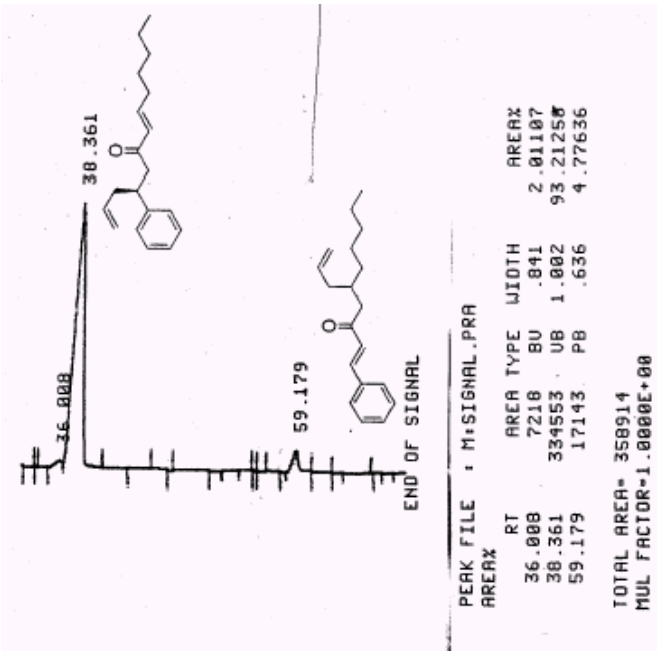
An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 3.0 mg (0.011 mmol) of bis(1,5-cyclooctadiene)nickel, 22.4 mg (0.0219 mmol) of chiral ligand **2.114**, and 0.44 mL of toluene in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 44.2 mg (0.263 mmol) of **2.51** was added followed by 50.0 mg (0.219 mmol) of **2.62**. The vial was capped, sealed with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for the time indicated in Table 2.7 (page 140). After this time period, degassed water (N_2 sparge) was added, and the mixture transferred to a separatory funnel with CH_2Cl_2. After swirling the layers, the organic layer was collected, and the aqueous layer washed with CH_2Cl_2 (2x). The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. Analysis of the unpurified reaction mixture using either GLC or ^{1}H NMR was used to determine the chemoselectivity of the reaction. Silica gel chromatography (hexanes/EtOAc) afforded 43.7 mg (0.162 mmol, 74%) of (*S*)-**2.64**.

(*S,E*)-4-Phenyltrideca-1,7-dien-6-one (2.64). An oil. R_f = 0.19 (SiO_2, 40:1 hexanes:EtOAc); IR (neat): 3030 (m), 2926 (s), 1697 (s), 1667 (s), 1452 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.14-7.24 (2H, m), 7.04-7.14 (3H, m), 6.65 (1H, dt, *J* = 16 Hz, *J* = 7.2

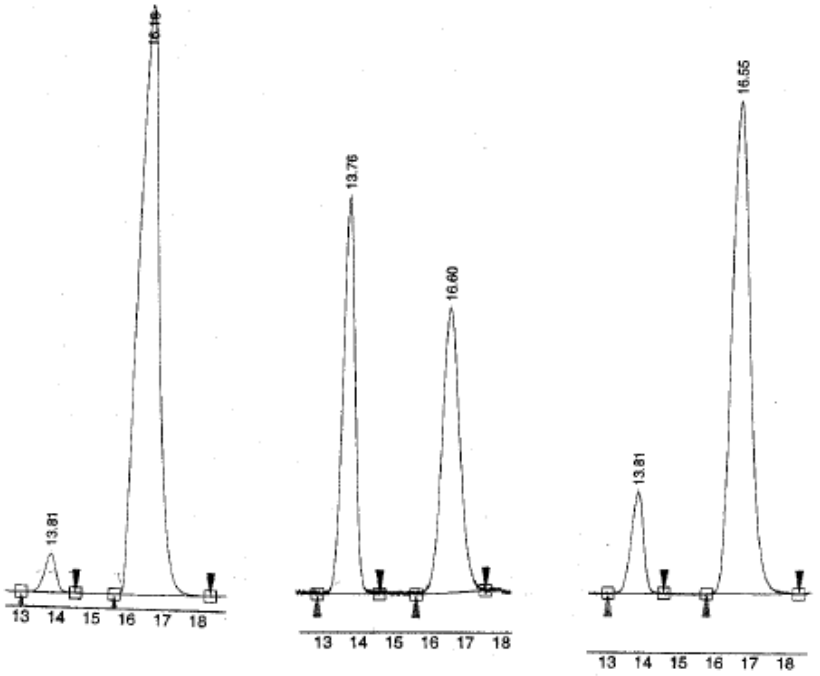
Hz), 5.92 (1H, d, *J* = 16 Hz), 5.56 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 7.2 Hz), 4.82-4.94 (2H, m) 3.22 (1H, p, *J* = 7.2 Hz), 2.76 (1H, app dd, *J* = 16 Hz, *J* = 6.6 Hz), 2.75 (1H, app dd, *J* = 16 Hz, *J* = 7.6 Hz), 2.30 (2H, t, *J* = 7.2 Hz), 2.06 (2H, q, *J* = 6.8 Hz), 1.32 (2H, p, *J* = 7.2 Hz), 1.10-1.28 (4H, m), 0.796 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 199.1, 147.6, 144.2, 136.2, 130.5, 128.3, 127.5, 126.2, 116.6, 46.04, 40.99, 40.62, 32.39, 31.31, 27.74, 22.42, 13.97. LRMS (ESI+) Calcd for $C_{19}H_{26}O$ $(M)^+$: 270.2, Found $(M)^+$: 270.7. $[\alpha]_D^{20}$ = +5.9 ^{o} (*c* = 1.0, $CHCl_3$).

Proof of stereochemistry. Chemoselectivity was determined using achiral GLC. Stereochemical ratios were determined by comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction. Absolute stereochemistry was determined by subjecting the conjugate allylation product to ring closing metathesis conditions using the Hoveyda-Grubbs' second generation catalyst, in CH_2Cl_2, to afford 5-phenyl-2-cycohexen-1-one (see page 358). The optical rotation was measured ($[\alpha]_D^{20}$ = +40^o (*c* = 0.5, $CHCl_3$)) and compared to the known literature value.[78]

Achiral GLC (Ultra 1, Hewlett-Packard, 140 ^{o}C) analysis of unpurified reaction mixture:



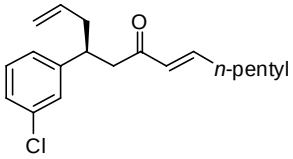
*Chiral SFC (AD-H, Chiralpak, 150 bar, 50^{o}C, flow = 1.0 mL/min, 2.0 % MeOH) analysis of conjugate allylation product (**2.64**):*



Allylation product

Racemic

Allylation product + racemic coinjection

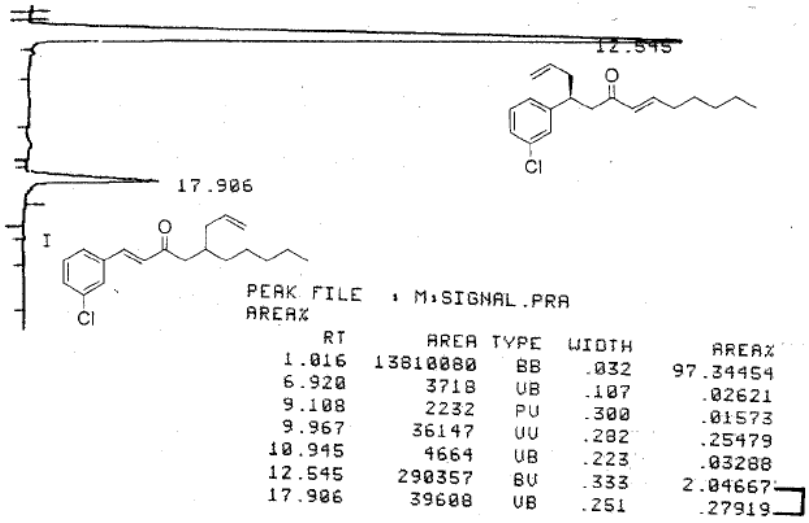


(*S*,*E*)-4-(3-Chlorophenyl)trideca-1,7-dien-6-one (2.132). Prepared according to the general procedure used to synthesize **2.64** on page 257. An oil. R_f (major) = 0.18 (SiO_2, 40:1 hexanes:EtOAc), R_f(minor) = 0.24 (SiO_2, 40:1 hexanes:EtOAc); IR (neat): 2957 (s), 2923 (s), 2853 (m), 1673 (s), 1624 (s), 1434 (m), 1367 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.00-7.20 (4H, m), 6.74 (1H, dt, *J* = 16 Hz, *J* = 6.8 Hz), 5.99 (1H, d, *J* = 16 Hz), 5.54 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 7.2 Hz), 4.87-5.03 (2H, m), 3.28 (1H, p, *J* = 7.2 Hz) 2.82 (1H, dd, *J* = 16 Hz, *J* = 6.0 Hz), 2.80 (1H, dd, *J* = 16 Hz, *J* = 7.6 Hz), 2.34 (2H, m), 2.14 (2H, q, *J* = 7.2 Hz), 1.40 (2H, p, *J* = 7.2 Hz), 1.15-1.35 (4H, m), 0.86 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 198.5, 147.9, 146.4, 135.7, 134.1, 130.4, 129.6, 127.5, 126.5, 125.9, 117.0, 45.65, 40.62, 40.48, 32.43, 31.33, 27.74, 22.43, 13.97. LRMS (ESI+) Calcd for $C_{19}H_{25}ClO$ $(M)^+$: 304.2, Found $(M)^+$: 304.7. $[\alpha]_D^{20}$ = +4.4° (*c* = 2.5, $CHCl_3$).

Proof of stereochemistry. Chemoselectivity was determined using achiral GLC (Note: the starting material had the same retention time as the major isomer. The reported ratios are calculated assuming 95% conversion as evident by the appearance of no starting material in the ^1H NMR spectrum of the unpurified reaction mixture.) Stereochemical ratios were determined by comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction. Absolute stereochemistry was determined by subjecting the conjugate allylation product to ring closing metathesis conditions using the Hoveyda-Grubbs' second generation catalyst, in CH_2Cl_2, to afford 5-(*m*-chlorophenyl)-2-cycohexen-1-one

(see page 358). The optical rotation was measured ($[\alpha]_D^{20}$ = +32° (*c* = 1.0, $CHCl_3$)) and compared to the known literature value.[50]

Achiral GLC (Ultra 1, Hewlett-Packard, 180 °C) analysis of unpurified reaction mixture:



PEAK FILE : M:SIGNAL.PRA
AREA%

RT	AREA	TYPE	WIDTH	AREA%
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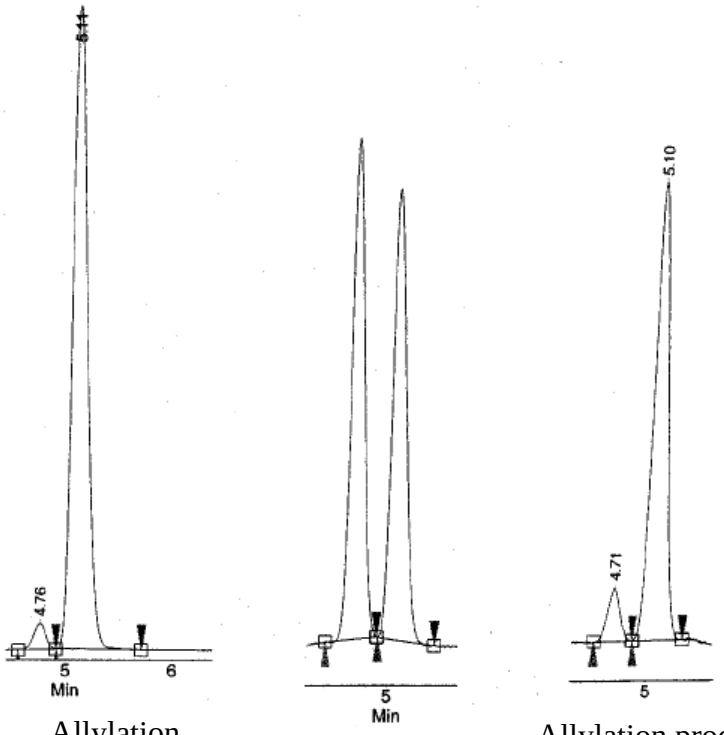
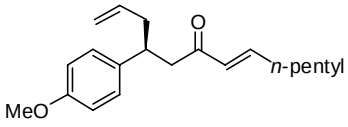
6.920	3718	VB	.107	.02621
9.108	2232	PU	.300	.01573
9.967	36147	VV	.282	.25479
10.945	4664	VB	.223	.03288
12.545	290357	BV	.333	2.04667
17.906	39608	VB	.251	.27919

*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 2.0 mL/min, 3.0 % MeOH) analysis of conjugate allylation product (**2.132**):*



Allylation product | Racemic | Allylation product + racemic coinjection



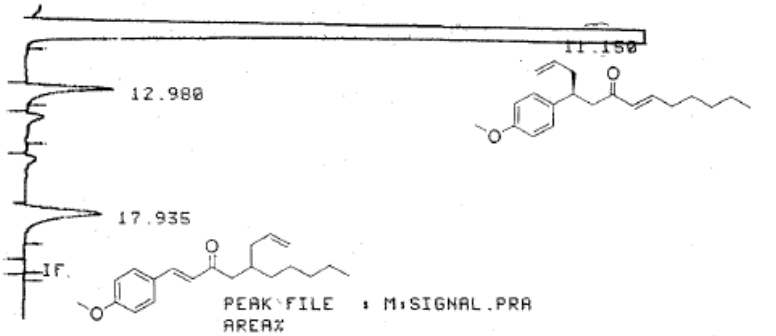
(*S*,*E*)-4-(4-Methoxyphenyl)trideca-1,7-dien-6-one (2.133). Prepared according to the general procedure used to synthesize **2.64** on page 257. An oil. R_f = 0.18 (SiO_2, 17:1 pentane:Et_2O); IR (neat): 3074 (w), 2962 (s), 2924 (s), 2861 (s), 2055 (w), 1879 (w), 1671 (s), 1620 (s), 1514 (s), 1464 (m), 1243 (s), 1180 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.08 (2H, d, *J* = 8 Hz), 6.79 (2H, d, *J* = 8 Hz), 6.72 (1H, dt, *J* = 16 Hz, *J* = 7.2 Hz), 5.98 (1H, d, *J* = 16 Hz), 5.63 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 6.8 Hz), 4.90-5.02 (2H, m) 3.75 (3H, s), 3.24 (1H, p, *J* = 7.6 Hz), 2.78 (2H, m), 2.34 (2H, t, *J* = 6.8 Hz), 2.13 (2H, q, *J* = 7.2 Hz), 1.39 (2H, p, *J* = 7.2

Hz), 1.18-1.34 (4 H, m), 0.863 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 199.3, 157.9, 147.5, 136.3, 136.2, 130.5, 128.3, 116.5, 113.7, 55.16, 46.33, 40.80, 40.28, 32.40, 31.33, 27.75, 22.42, 13.99. LRMS (ESI+) Calcd for $C_{20}H_{28}O_2$ $(M)^+$: 300.2, Found $(M)^+$: 300.8. $[\alpha]_D^{20}$ = +9.5° (c = 3.0, $CHCl_3$).

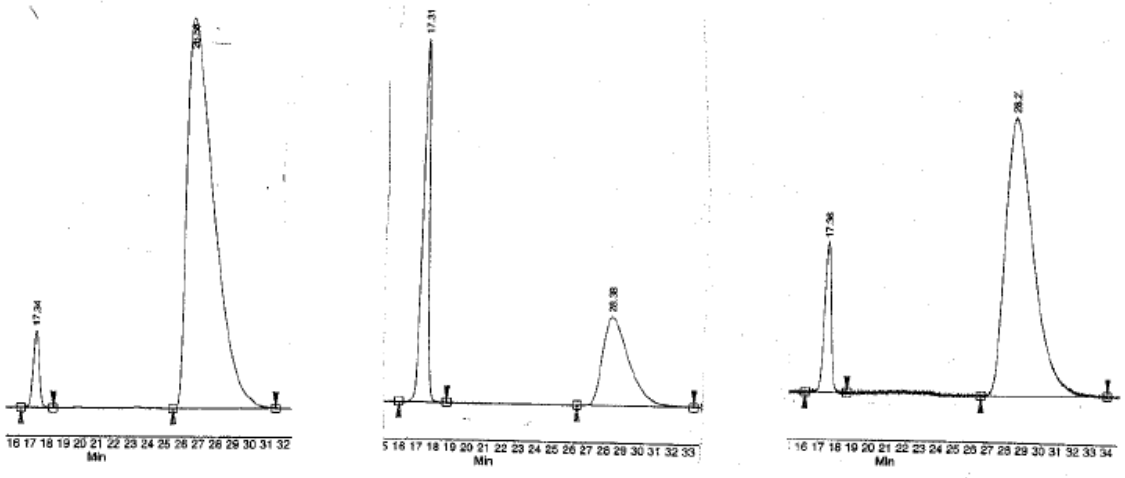
Proof of stereochemistry. Chemoselectivity was determined using achiral GLC. Stereochemical ratios were determined by comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction. Absolute stereochemistry was determined by subjecting the conjugate allylation product to ring closing metathesis conditions using the Hoveyda-Grubbs' second generation catalyst, in CH_2Cl_2, to afford 5-(*p*-methoxyphenyl)-2-cycohexen-1-one (see page 358). Subsequent 1,4-reduction with Pd/C and H_2 gave the corresponding saturated cyclohexanone derivative.[50] The optical rotation was measured ($[\alpha]_D^{20}$ = -12° (c = 1.0, $CHCl_3$)) and compared to the known literature value.[1]

[1] Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957.

Achiral GLC (Ultra 1, Hewlett-Packard, 190 ^{o}C) analysis of unpurified reaction mixture:



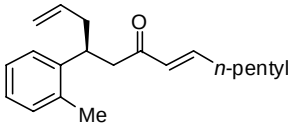
*Chiral SFC (AD-H, Chiralpak, 150 bar, 50^{o}C, flow = 1.0 mL/min, 3.0 % MeOH) analysis of conjugate allylation product (**2.133**):*



Allylation product

Racemic

Allylation product+ racemic coinjection

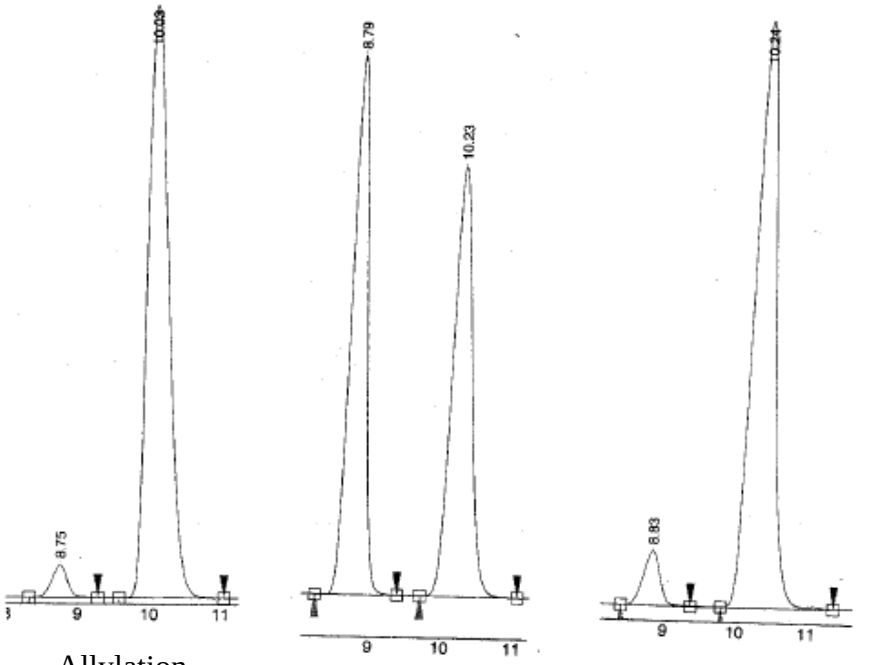


(*S*,*E*)-4-*o*-Tolyltrideca-1,7-dien-6-one (2.134). Prepared according to the general procedure used to synthesize **2.64** on page 257. An oil. R_f = 0.19 (SiO_2, 30:1 hexanes:EtOAc); IR (neat): 3069 (m), 3018 (m), 2930 (s), 2861 (s), 1829 (w), 1671 (s), 1627 (s), 1457 (m), 1262 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.00-7.18 (4H, m), 6.73 (1H, dt, *J* = 16 Hz, *J* = 7.2 Hz), 5.99 (1H, dt, *J* = 16 Hz, *J* = 1.2 Hz), 5.63 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 6.8 Hz), 4.88-5.02 (2H, m) 3.60 (1H, p, *J* = 6.8 Hz), 2.83 (2H, d, *J* = 6.8 Hz), 2.35 (5H, m), 2.13 (2H, q, *J* = 6.8 Hz), 1.39 (2H, p, *J* = 7.2 Hz), 1.18-1.35 (4 H, m), 0.87 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 199.2, 147.5, 142.5, 136.2, 135.9, 130.5, 130.3, 126.0, 125.9, 125.7, 116.5, 45.79, 40.44, 35.65, 32.40, 31.32, 27.76, 22.44, 19.84, 13.97. LRMS (ESI+) Calcd for $C_{20}H_{28}O$ $(M)^+$: 284.2, Found $(M)^+$: 284.8. $[\alpha]_D^{20}$ = +6.4° (*c* = 0.6, $CHCl_3$).

Proof of stereochemistry. Chemoselectivity was determined using ^1H NMR spectroscopy; the minor isomer was not observed in the ^1H NMR spectrum of the unpurified reaction mixture. Stereochemical ratios were determined by comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction. Absolute stereochemistry was determined by subjecting the conjugate allylation product to ring closing metathesis conditions using the Hoveyda-Grubbs' second generation catalyst, in CH_2Cl_2, to afford 5-(*o*-tolyl)-2-cycohexen-1-one (see page 358). Subsequent 1,4-reduction with Pd/C and H_2 gave the corresponding saturated cyclohexanone derivative.[50]

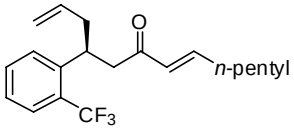
The optical rotation was measured ($[\alpha]_D^{20}$ = -37° (*c* = 0.8, CCl_4)) and compared to the known literature value.[2]

*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 1.0 mL/min, 3.0 % MeOH) analysis of conjugate allylation product (**2.134**):*



Allylation product | Racemic | Allylation product + racemic coinjection

[2] Ek, M.; Ahlberg, P. *Acta. Chem. Scand. Ser. B* **1984**, *38*, 211.

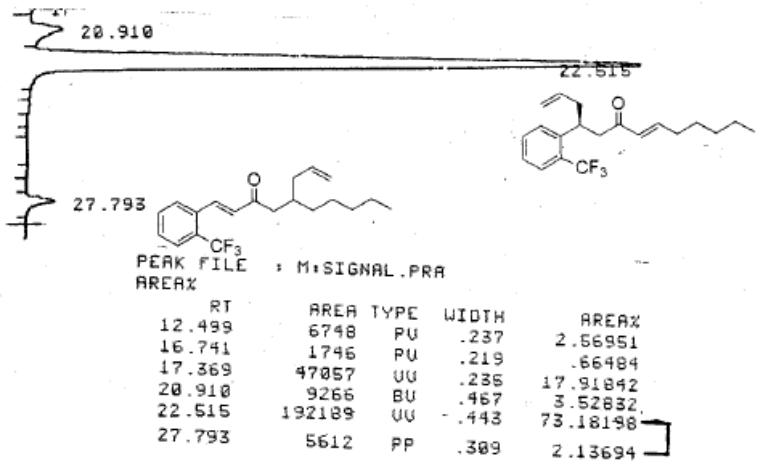


(*S*,*E*)-4-[2-(Trifluoromethyl)phenyl]trideca-1,7-dien-6-one (2.135). Prepared according to the general procedure used to synthesize **2.64** on page 257. An oil. R_f = 0.18 (SiO_2, 30:1 hexanes:EtOAc); IR (neat): 2961 (s), 2930 (s), 2861 (s), 1828 (w), 1696 (s), 1457 (m), 1312 (s), 1155 (s), 1117 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60 (1H, d, *J* = 8.0 Hz), 7.48 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.0 Hz), 7.26 (1H, t, *J* = 7.5 Hz), 6.76 (1H, dt, *J* = 16 Hz, *J* = 7 Hz), 6.03 (1H, d, *J* = 16 Hz), 5.61 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 7 Hz), 4.93 (1H, d, *J* = 17 Hz), 4.91 (1H, d, *J* = 10 Hz), 3.74 (1H, p, *J* = 7 Hz), 2.84 (1H, dd, *J* = 16 Hz, *J* = 7.5 Hz), 2.80 (1H, dd, *J* = 16 Hz, *J* = 6.0 Hz), 2.40 (2H, t, *J* = 7.5 Hz), 2.15 (2H, q, *J* = 7.0 Hz), 1.40 (2H, p, *J* = 7.5 Hz), 1.18-1.35 (4 H, m), 0.87 (3H, t, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$): δ 198.3, 148.0, 143.3, 135.6, 131.8, 130.0, 128.5 (q, $^2J_{CF}$ = 29 Hz), 128.0, 126.2, 125.9 (q, $^3J_{CF}$ = 6.1 Hz), 124.4 (q, $^1J_{CF}$ = 272 Hz), 117.0, 46.45, 40.43, 36.08, 32.38, 31.28, 27.69, 22.39, 13.90. ^{19}F NMR ($CDCl_3$): δ -59.81. LRMS (ESI+) Calcd for $C_{20}H_{25}F_3O$ $(M)^+$: 338.2, Found $(M)^+$: 338.8.

Proof of stereochemistry. Chemoselectivity was determined using achiral GLC. To determine the enantiomeric purity, the title compound was subjected to ring-closing metathesis (RCM) conditions using the Hoveyda-Grubbs' second generation catalyst, in CH_2Cl_2, to afford 5-(*o*-trifluoromethylphenyl)-2-cycohexen-1-one (see page 358). This derivative was then analyzed by chiral SFC. Stereochemical ratios were determined in comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction followed by

RCM. Absolute stereochemistry was assumed to be analogous to the configuration determined for others.

Achiral GLC (Ultra 1, Hewlett-Packard, 150 ^{o}C) analysis of unpurified reaction mixture:



PEAK FILE : M:SIGNAL.PRA
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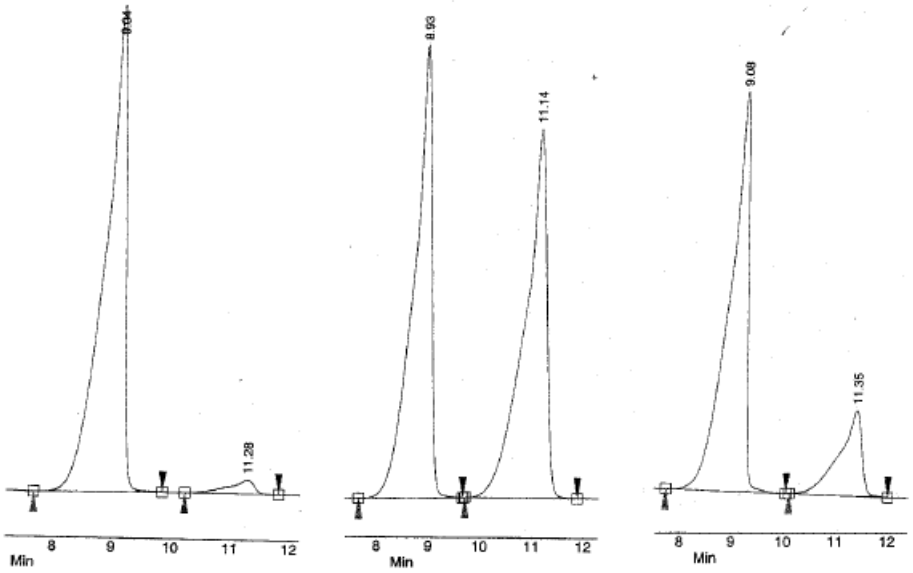
17.369	47057	VV	.235	17.91842
20.910	9266	BV	.467	3.52832
22.515	192189	VV	.443	73.18198
27.793	5612	PP	.389	2.13694

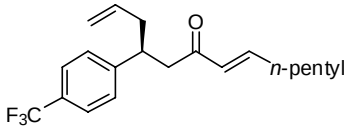
Chiral SFC ((R,R)-Whelk-O, Pirkle Covalent, 150 bar, 50^{o}C, flow = 2.0 mL/min, 2.0 % MeOH) analysis of conjugate allylation-RCM product:



Allylation-RCM product

Racemic

Allylation-RCM product + racemic coinjection

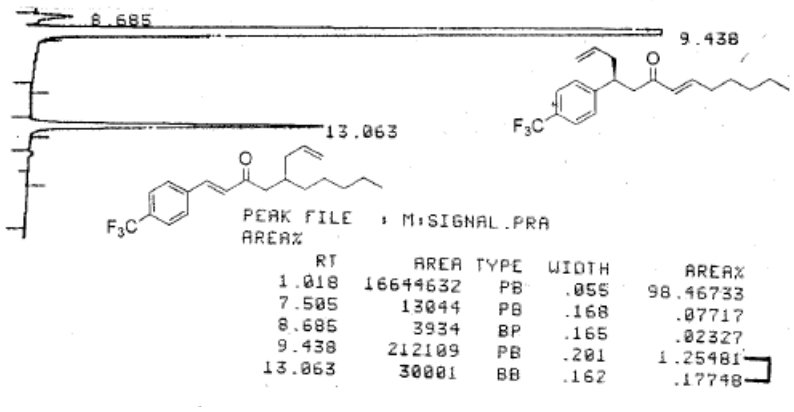


(*S*,*E*)-4-[4-(Trifluoromethyl)phenyl]trideca-1,7-dien-6-one (2.136). Prepared according to the general procedure used to synthesize **2.64** on page 257. An oil. R_f (major) = 0.19 (SiO_2, 30:1 hexanes:EtOAc), R_f (minor) = 0.24 (SiO_2, 30:1 hexanes:EtOAc); IR (neat): 2961 (s), 2930 (s), 2854 (m), 1702 (m), 1677 (s), 1620 (s), 1331 (s), 1167 (s), 1123 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.51 (2H, d, *J* = 8.0 Hz), 7.29 (2H, d, *J* = 8.0 Hz), 6.74 (1H, dt, *J* = 16 Hz, *J* = 7 Hz), 5.99 (1H, d, *J* = 16 Hz), 5.61 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 7 Hz), 4.96 (1H, d, *J* = 17 Hz), 4.95 (1H, d, *J* = 10 Hz), 3.38 (1H, p, *J* = 7.5 Hz), 2.86 (1H, dd, *J* = 17 Hz, *J* = 7.0 Hz), 2.83 (1H, dd, *J* = 17 Hz, *J* = 7.5 Hz), 2.39 (1H, dd, *J* = 14 Hz, *J* = 7.0 Hz), 2.36 (1H, dd, *J* = 14 Hz, *J* =7.0 Hz), 2.14 (2H, q, *J* = 7.0 Hz), 1.39 (2H, p, *J* = 7.0 Hz), 1.20-1.33 (4 H, m), 0.86 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 198.5, 148.4, 148.0, 135.6, 130.4, 128.6 (q, $^2J_{CF}$ = 32 Hz), 127.9, 125.3 (q, $^3J_{CF}$ = 3.9 Hz), 124.2 (q, $^1J_{CF}$ = 271 Hz), 117.2, 45.60, 40.65, 40.39, 32.38, 31.30, 27.69, 22.36, 13.89. ^{19}F NMR ($CDCl_3$): δ -63.72. LRMS (ESI+) Calcd for $C_{20}H_{25}F_3O$ $(M)^+$: 338.2, Found $(M)^+$: 338.8.

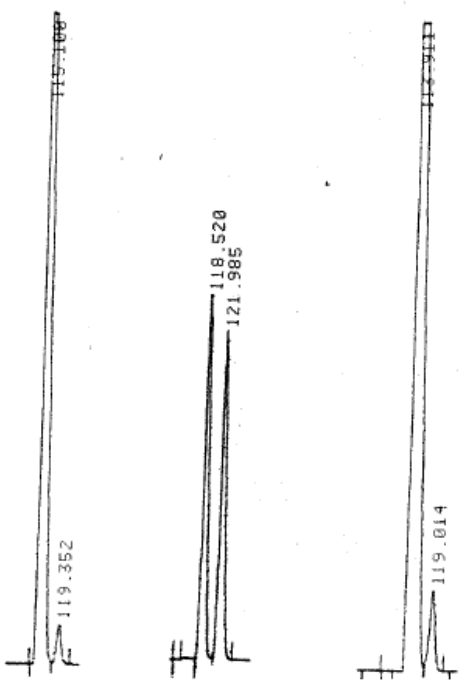
Proof of stereochemistry. Chemoselectivity was determined using achiral GLC. To determine the enantiomeric purity, the title compound was subjected to ring-closing metathesis (RCM) conditions using the Hoveyda-Grubbs' second generation catalyst, in CH_2Cl_2, to afford 5-(*p*-trifluoromethylphenyl)-2-cyclohexen-1-one (see page 358). This derivative was then analyzed by chiral GLC. Stereochemical ratios were determined in comparison with authentic racemic material prepared using either triphenylphosphine or

triphenylphosphite as the achiral ligand in the conjugate allylation reaction followed by RCM. Absolute stereochemistry was determined by comparing the optical rotation ($[\alpha]_D^{20} = +37^o$ (c = 1.0, $CHCl_3$)) of the RCM product to the known value.[50]

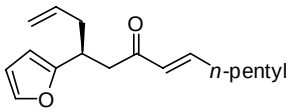
Achiral GLC (Ultra 1, Hewlett-Packard, 170 °C) analysis of unpurified reaction mixture:



Chiral GLC (β-dex, Supelco, 130°C) analysis of conjugate allylation-RCM product:



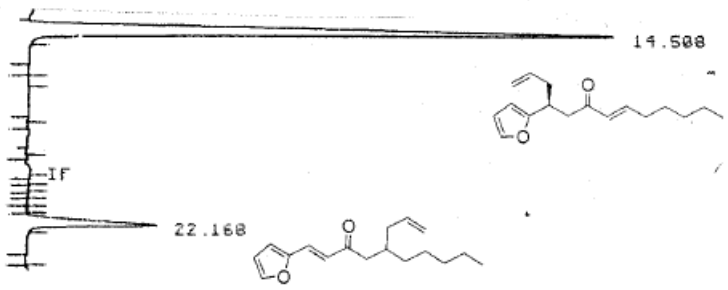
Allylation-RCM product | Racemic | Allylation-RCM product + racemic coinjection



(*S*,*E*)-4-(Furan-2-yl)trideca-1,7-dien-6-one (2.140). Prepared according to the general procedure used to synthesize **2.64** on page 257. An oil. Isolated as an inseparable mixture of constitutional isomers. R_f = 0.16 (SiO_2, 30:1 hexanes:EtOAc, both constitutional isomers); IR (neat): 3074 (w), 2955 (s), 2930 (s), 2854 (m), 1671 (s), 1626 (s), 1444 (m), 1362 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.47 (1H, d, *J* = 3.2 Hz, minor), 7.28 (1H, d, *J* = 16 Hz, minor), 7.27 (1H, dd, *J* = 2.0 Hz, *J* = 1.2 Hz, major), 6.77 (1H, dt, *J* = 16 Hz, *J* = 7.2 Hz, major), 6.64 (1H, d, *J* = 2.0 Hz, minor), 6.61 (1H, d, *J* = 16 Hz, minor), 6.46 (1H, dd, *J* = 3.2 Hz, *J* = 2.0 Hz, minor), 6.23 (1H, dd, *J* = 3.2 Hz, *J* = 2.0 Hz, major), 6.03 (1H, dt, *J* = 16 Hz, *J* = 1.2 Hz, major), 5.98 (1H, d, *J* = 3.2 Hz, major), 5.67 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 7.2 Hz, major), 4.94-5.04 (4H, m, major + minor), 3.43 (1H, p, *J* = 7.2 Hz, major), 2.87 (1H, dd. *J* = 16 Hz, *J* = 7.2 Hz, major), 2.75 (1H, dd, *J* = 16 Hz, *J* = 6.8 Hz, major), 2.53 (1H, dd, *J* = 16 Hz, *J* = 6.4 Hz, minor), 2.45 (1H, dd, *J* = 16 Hz, *J* = 5.6 Hz, minor), 2.28-2.46 (3H, m, major + minor), 1.42 (2H, p, *J* = 7.6 Hz, major), 1.18-1.35 (12H, m, major + minor), 0.87 (3H, t, *J* = 6.8 Hz, major), 0.85 (3H, t, *J* = 7.2 Hz, minor); ^{13}C NMR ($CDCl_3$): δ (major) 198.7, 157.1, 147.8, 140.9, 135.7, 130.4, 116.9, 109.9, 105.1, 43.06, 38.00, 34.27, 32.46, 31.34, 27.76, 22.45, 13.98. LRMS (ESI+) Calcd for $C_{17}H_{24}O_2$ $(M)^+$: 260.2, Found $(M)^+$: 260.7.

Proof of stereochemistry. Chemoselectivity was determined using achiral GLC. Stereochemical ratios were determined by comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction. Absolute stereochemistry was assumed to be analogous to the configuration determined for others.

Achiral GLC (Ultra 1, Hewlett-Packard, 145 ^{o}C) analysis of unpurified reaction mixture:



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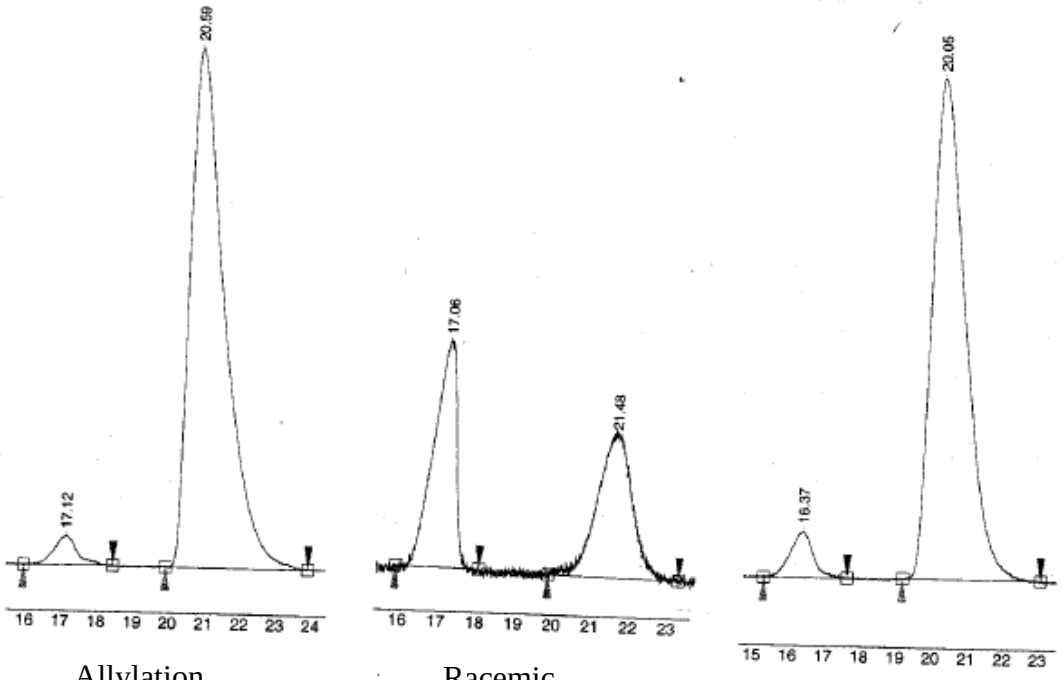
22.168	41356	BB	.258	.11412
45.399	30276	BB	.559	.08355

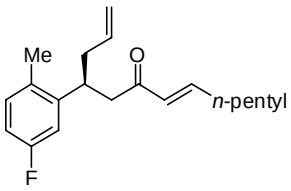
*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 1.0 mL/min, 1.0 % MeOH) analysis of conjugate allylation product (**2.140**):*



Allylation product

Racemic

Allylation product + racemic coinjection

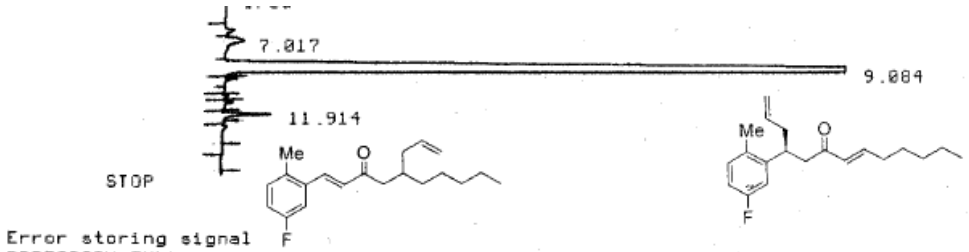


(*S*,*E*)-4-(5-Fluoro-2-methylphenyl)trideca-1,7-dien-6-one (2.137). Prepared according to the general procedure used to synthesize **2.64** on page 257. An oil. R_f = 0.18 (SiO_2, 30:1 hexanes:EtOAc); IR (neat): 3075 (w), 3031 (w), 2955 (s), 2924 (s), 2861 (s), 1841 (w), 1697 (s), 1665 (s), 1621 (s), 1495 (s), 1457 (m), 1237 (m) cm^{-1}; ^1H NMR ($CDCl_3$): 7.03 (1H, dd, *J* = 8.4 Hz, *J* = 6.0 Hz), 6.68-6.85 (3H, m), 5.99 (1H, dt, *J* = 16 Hz, *J* = 1.6 Hz), 5.60 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 6.8 Hz), 4.96 (1H, d, *J* = 17 Hz), 4.93 (1H, d, *J* =

10 Hz), 3.57 (1H, p, J = 7.2 Hz), 2.82 (1H, app dd, J = 16 Hz, J = 6.4 Hz), 2.78 (1H, app dd, J = 16 Hz, J = 7.2 Hz), 2.22-2.39 (5H, m), 2.13 (2H, q, J = 7.2 Hz), 1.40 (2H, p, J = 7.2 Hz), 1.17-1.34 (4H, m), 0.86 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 198.6, 161.4 (d, $^1J_{CF}$ = 241 Hz), 147.7, 144.7 (d, $^3J_{CF}$ = 6.2 Hz), 135.7, 131.42, 131.36 (d, $^3J_{CF}$ = 4.7 Hz), 130.4, 116.9, 112.5 (d, $^2J_{CF}$ = 21 Hz), 112.4 (d, $^2J_{CF}$ = 21 Hz), 45.43, 40.29, 35.73, 32.37, 31.28, 27.70, 22.39, 19.06, 13.91; ^{19}F NMR ($CDCl_3$): δ 93.93 (m). LRMS (ESI+) Calcd for $C_{20}H_{27}FO$ $(M + Na)^+$: 325.2, Found $(M + Na)^+$: 324.7.

Proof of stereochemistry. GLC analysis of the unpurified reaction mixture was used to determine the chemoselectivity of the reaction (Note: the starting material had the same retention time as the major isomer. The reported ratios are calculated assuming 95% conversion as evident by the appearance of no starting material in the ^{1}H NMR spectrum of the unpurified reaction mixture.) The enantioselectivity of the reaction was determined by measuring the enantiomeric excess of the cyclic enone formed after ring-closing metathesis (see page 362). Stereochemical ratios were determined in comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction followed by RCM. Absolute stereochemistry was assumed to be analogous to the configuration determined for others.

Achiral GLC (Ultra 1, Hewlett-Packard, 180 °C) analysis of unpurified reaction mixture:

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DIRECTORY FULL
Storing processed peaks to M:SIGNAL   .PRA

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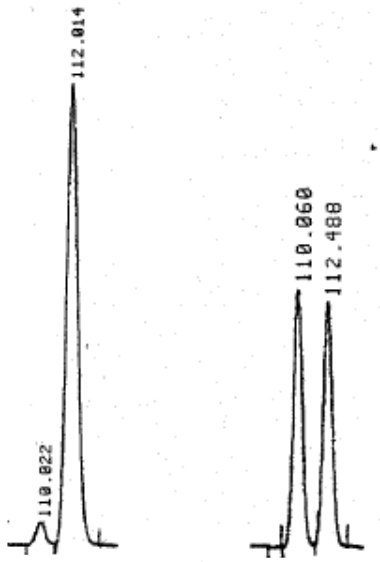
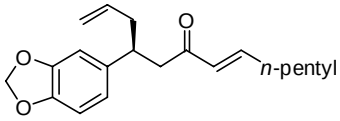
53:1 ⇒ 51:1 @85°C conv.

*Chiral GLC (β-dex, Supelco, 135°C) analysis of conjugate allylation-RCM product (**2.142**):*



Allylation-RCM product

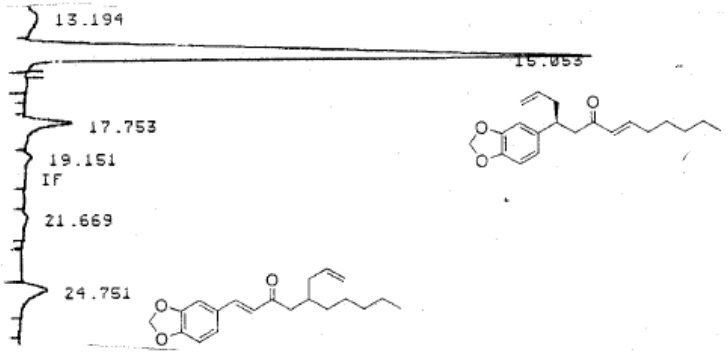
Racemic



(*S*,*E*)-4-(Benzo[*d*][1,3]dioxol-5-yl)trideca-1,7-dien-6-one (2.138). Prepared according to the general procedure used to synthesize **2.64** on page 257. An oil. R_f = 0.27 (SiO_2, 15:1 pentane:Et_2O); IR (neat): 3075 (m), 2962 (s), 2930 (s), 2855 (s), 1841 (w), 1671 (s), 1627 (s), 1483 (s), 1444 (s), 1350 (m), 1243 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.55-6.80 (4H, m), 5.99 (1H, d, *J* = 16 Hz), 5.89 (2H, s), 5.62 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 7.2 Hz), 4.90-5.05 (2H, m), 3.21 (1H, p, *J* = 7.2 Hz), 2.76 (2H, d, *J* = 6.8 Hz), 2.31 (2H, m), 2.13 (2H, q, *J* = 7.6 Hz), 1.40 (2H, p, *J* = 7.2 Hz), 1.16-1.36 (4H, m), 0.86 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 199.0, 147.6, 147.5, 145.8, 138.1, 136.2, 130.5, 120.5, 116.6, 108.1, 107.7, 100.8, 46.27, 40.84, 40.83, 32.41, 31.33, 27.76, 22.42, 13.96. LRMS (ESI+) Calcd for $C_{20}H_{26}O_3$ $(M)^+$: 314.2, Found $(M)^+$: 314.8. $[\alpha]_D^{20}$ = +11° (*c* = 3.0, $CHCl_3$).

Proof of stereochemistry. Chemoselectivity was determined using achiral GLC. Stereochemical ratios were determined in comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction. Absolute stereochemistry was assumed to be analogous to the configuration determined for others.

Achiral GLC (Ultra 1, Hewlett-Packard, 190 ^{o}C) analysis of unpurified reaction mixture:



PEAK FILE : M:SIGNAL.PRA
AREA%

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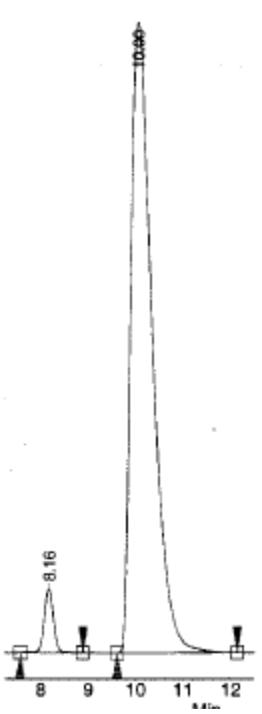
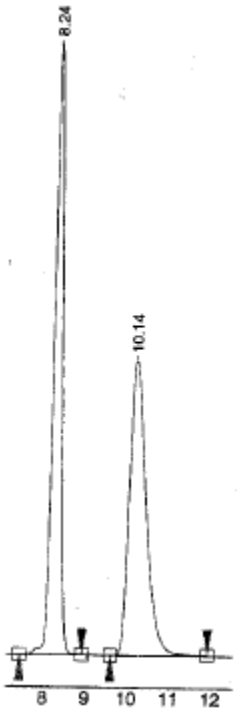
13.194	14186	VV	.844	3.07796
15.053	336979	VB	.443	73.11485
17.753	23562	PV	.369	5.11228
19.151	5306	VV	.494	1.15125
21.669	3220	VV	.459	.69865
24.751	14843	BP	.470	3.22051

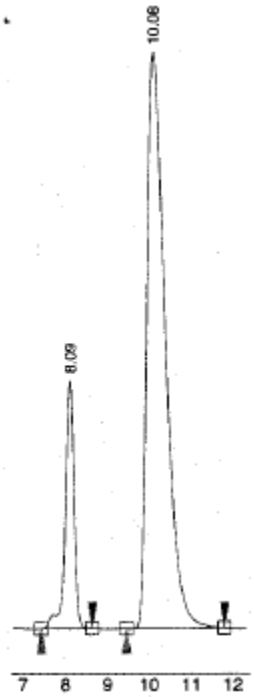
*Chiral SFC (AD-H, Chiralpak, 150 bar, 50^{o}C, flow = 2.0 mL/min, 3.0 % MeOH) analysis of conjugate allylation product (**2.138**):*



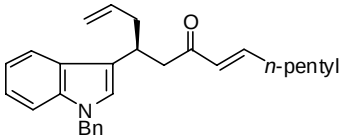
Allylation product



Racemic



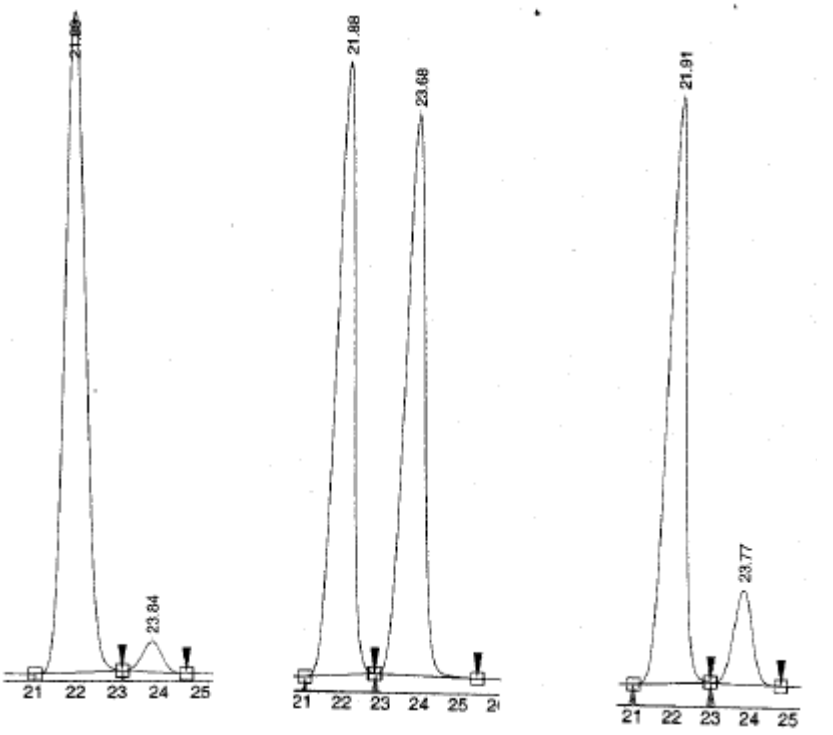
Allylation product + racemic coinjection



(*S*,*E*)-4-(1-Benzyl-1*H*-indol-3-yl)trideca-1,7-dien-6-one (2.139). Prepared according to the general procedure used to synthesize **2.64** on page 257. An oil. R_f = 0.10 (SiO_2, 2:1 pentane:CH_2Cl_2); IR (neat): 3062 (m), 2924 (s), 2848 (s), 1697 (s), 1671 (s), 1463 (s), 1350 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.68 (1H, d, *J* = 7.5 Hz), 7.00-7.32 (8H, m), 6.91 (1H, s), 6.72 (1H, dt, *J* = 16 Hz, *J* = 6.8 Hz), 6.02 (1H, d, *J* = 16 Hz), 5.75 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 7.2 Hz), 5.25 (2H, s), 5.00 (1H, d, *J* = 17 Hz), 4.95 (1H, d, *J* = 10 Hz), 3.66 (1H, p, *J* = 7.2 Hz), 2.97 (2H, dd, *J* = 16 Hz, *J* = 7.6 Hz), 2.93 (1H, dd, *J* =16 Hz, *J* = 7.6 Hz), 2.56 (1H, dd, *J* = 14 Hz, *J* = 6.8 Hz), 2.52 (1H, dd, *J* = 14 Hz, *J* = 6.4 Hz), 2.09 (2H, q, *J* = 6.8 Hz), 1.15-1.40 (6H, m), 0.87 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 199.8, 147.4, 137.6, 136.7, 130.5, 128.6, 127.4, 127.2, 126.5, 125.4, 121.6, 119.5, 118.9, 118.0, 116.3, 109.7, 49.84, 45.36, 39.74, 32.65, 32.38, 31.31, 27.68, 22.41, 13.97. LRMS (ESI+) Calcd for $C_{28}H_{33}NO$ $(M)^+$: 399.3, Found $(M)^+$: 399.8. $[\alpha]_D^{20}$ = +15° (*c* = 3.5, $CHCl_3$).

Proof of stereochemistry. Chemoselectivity was determined using ^1H NMR spectroscopy; the minor isomer was not observed in the ^1H NMR spectrum of the unpurified reaction mixture. Stereochemical ratios were determined in comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction. Absolute stereochemistry was assumed to be analogous to the configuration determined for others.

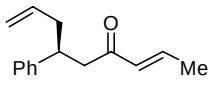
*Chiral SFC (AS-H, Chiralpak, 150 bar, 50°C, flow = 1.0 mL/min, 4.0 % MeOH) analysis of conjugate allylation product (**2.139**):*



Allylation product

Racemic

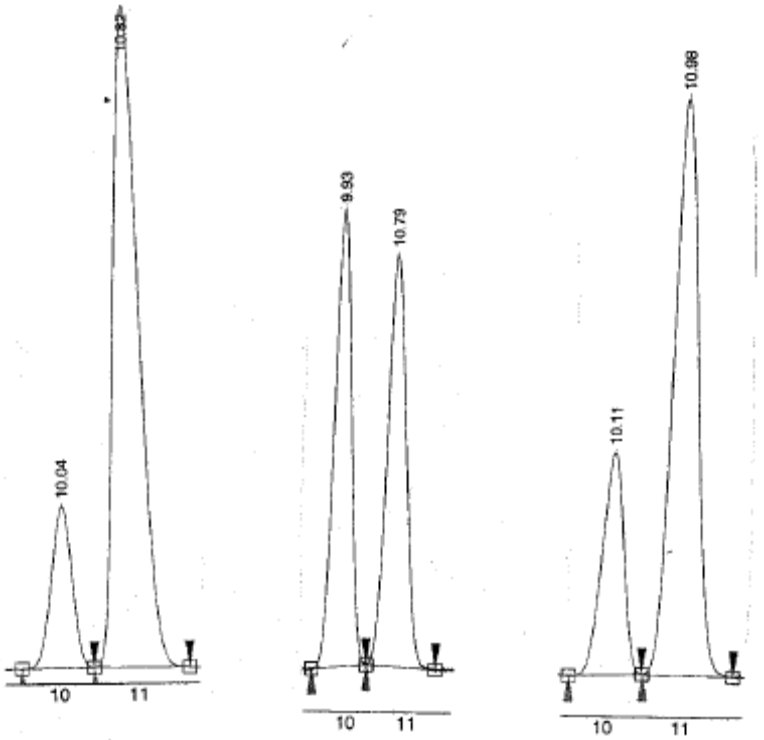
Allylation product + racemic coinjection



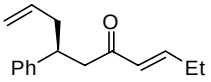
(*S*,*E*)-6-Phenylnona-2,8-dien-4-one (2.210). Prepared according to the general procedure used to synthesize **2.64** on page 257. An oil. R_f = 0.20 (SiO_2, 15:1 pentane:Et_2O); IR (neat): 3069 (m), 3024 (m), 2911 (m), 1697 (s), 1671 (s), 1627 (s), 1495 (m), 1439 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.10-7.35 (5H, m), 6.76 (1H, dq, *J* = 16 Hz, *J* = 6.8 Hz), 6.03 (1H, dq, *J* = 16 Hz, *J* = 1.6 Hz), 5.63 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 6.8 Hz), 4.86-5.05 (2H, m), 3.30 (1H, p, *J* = 7.2 Hz), 2.83 (1H, dd, *J* = 16 Hz, *J* = 6.8 Hz), 2.81 (1H, dd, *J* = 16 Hz, *J* = 7.2 Hz), 2.37 (2H, t, *J* = 7.2 Hz), 1.82 (3H, dd, *J* = 6.8 Hz, *J* = 1.6 Hz); ^{13}C NMR ($CDCl_3$): δ 198.7, 144.2, 142.4, 136.2, 132.1, 128.3, 127.5, 126.2, 116.6, 46.03, 40.85, 40.60, 18.18. LRMS (ESI+) Calcd for $C_{15}H_{18}O$ $(M + Na)^+$: 237.1, Found $(M + Na)^+$: 236.7. $[\alpha]_D^{20}$ = +9.3° (*c* = 2.5, $CHCl_3$).

Proof of stereochemistry. Chemoselectivity was determined by ^1H NMR spectroscopy; the minor isomer was not observed in the ^1H NMR spectrum of the unpurified reaction mixture. Stereochemical ratios were determined in comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction. Absolute stereochemistry was determined by subjecting the conjugate allylation product to ring-closing metathesis conditions using the Hoveyda-Grubbs second generation catalyst, in CH_2Cl_2, to afford 5-phenyl-2-cycohexen-1-one (see page 358). The optical rotation was measured ($[\alpha]_D^{20}$ = +37° (*c* = 0.5, $CHCl_3$)) and compared to the known literature value.[78]

*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 1.0 mL/min, 2.0 % MeOH) analysis of conjugate allylation product (**2.210**):*



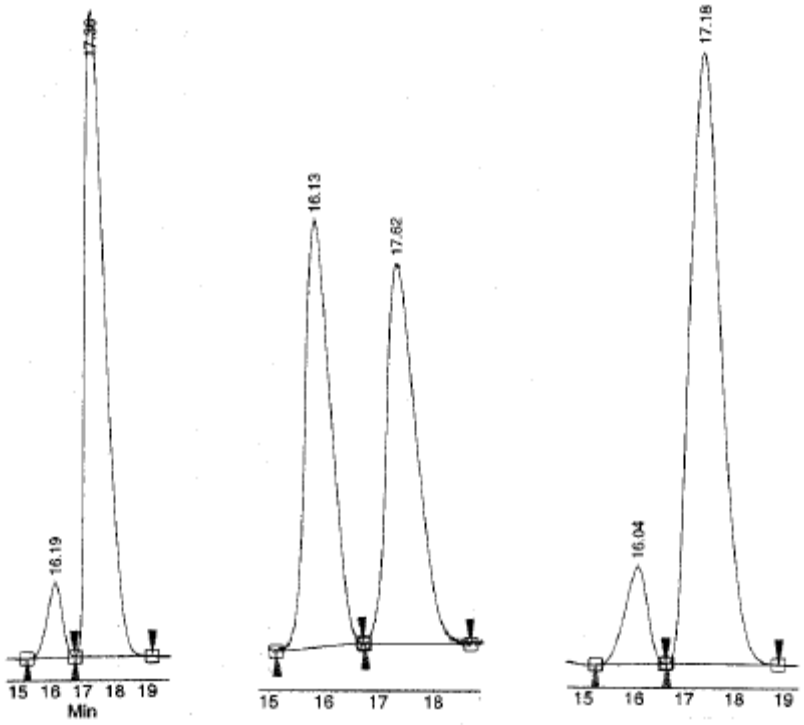
Allylation product | Racemic | Allylation product + racemic coinjection



(*S*,*E*)-7-Phenyldeca-3,9-dien-5-one (2.211). Prepared according to the general procedure used to synthesize **2.64** on page 257. An oil. R_f = 0.22 (SiO_2, 20:1 hexanes:EtOAc); IR (neat): 3068 (m), 3024 (m), 2968 (s), 2924 (s), 1948 (w), 1804 (w), 1697 (s), 1627 (s), 1451 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.12-7.32 (5H, m), 6.78 (1H, dt, *J* = 16 Hz, *J* = 6.8 Hz), 5.99 (1H, d, *J* = 16 Hz), 5.63 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 6.8 Hz), 4.86-5.05 (2H, m) 3.29 (1H, p, *J* = 7.2 Hz), 2.84 (1H, app dd, *J* = 16 Hz, *J* = 6.8 Hz), 2.82 (1H, app dd, *J* = 16 Hz, *J* = 7.2 Hz), 2.37 (2H, t, *J* = 7.2 Hz), 2.16 (2H, p, *J* = 7.2 Hz), 1.00 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 199.1, 148.7, 144.2, 136.2, 129.6, 128.3, 127.5, 126.3, 116.6, 46.12, 40.96, 40.63, 25.50, 12.25. LRMS (ESI+) Calcd for $C_{16}H_{20}O$ $(M + Na)^+$: 251.2, Found $(M + Na)^+$: 250.7. $[\alpha]_D^{20}$ = $+8.8^o$ (*c* = 1.0, $CHCl_3$).

Proof of stereochemistry. Chemoselectivity was determined by ^1H NMR spectroscopy; the minor isomer was not observed in the ^1H NMR spectrum of the unpurified reaction mixture. Stereochemical ratios were determined in comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction. Absolute stereochemistry was determined by subjecting the conjugate allylation product to ring closing metathesis conditions using the Hoveyda-Grubbs' second generation catalyst, in CH_2Cl_2, to afford 5-phenyl-2-cycohexen-1-one (see page 358). The optical rotation was measured ($[\alpha]_D^{20}$ = $+41^o$ (*c* = 0.5, $CHCl_3$)) and compared to the known literature value.[78]

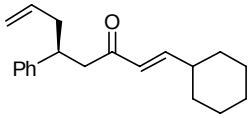
*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 1.0 mL/min, 1.0 % MeOH) analysis of conjugate allylation product (**2.211**):*



Allylation product

Racemic

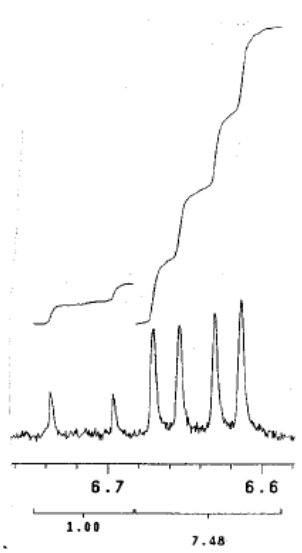
Allylation product + racemic coinjection



(*S*,*E*)-1-Cyclohexyl-5-phenylocta-1,7-dien-3-one (2.212). Prepared according to the general procedure used to synthesize **2.64** on page 257. An oil. Isolated as an inseparable mixture of constitutional isomers. R_f = 0.19 (SiO_2, 30:1 hexanes:EtOAc, major+minor); IR (neat): 3069 (m), 3024 (m), 2924 (s), 2855 (s), 1948 (w), 1810 (w), 1700 (s), 1671 (s), 1627 (s), 1445 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.10-7.30 (5H, m), 6.64 (1H, dd, *J* = 16 Hz, *J* = 6.8 Hz), 5.93 (1H, dd, *J* = 16 Hz, *J* = 1.2 Hz), 5.63 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 6.8 Hz), 4.85-5.05 (2H, m) 3.28 (1H, p, *J* = 7.2 Hz), 2.83 (1H, dd, *J* = 16 Hz, *J* = 6.8 Hz), 2.81 (1H, dd, *J* = 16 Hz, *J* = 7.6 Hz), 2.37 (2H, t, *J* = 7.2 Hz), 2.05 (1H, m), 0.92-1.80 (10H, m); ^{13}C NMR ($CDCl_3$, major + minor isomers): δ 200.4, 199.4, 152.3, 144.2, 142.0, 137.4, 136.2, 134.6, 130.2, 128.8, 128.3, 128.2, 128.0, 127.5, 126.5, 126.2, 116.5, 116.2, 46.13, 42.58, 41.09, 40.59, 40.54, 40.44, 39.22, 35.91, 37.74, 30.09, 29.71, 26.72, 25.92, 25.69. LRMS (ESI+) Calcd for $C_{20}H_{26}O$ $(M + Na)^+$: 305.2, Found $(M + Na)^+$: 304.8.

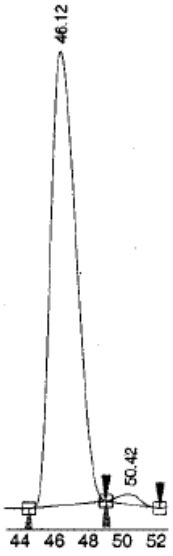
Proof of stereochemistry. Chemoselectivity was determined by ^1H NMR spectroscopy. Stereochemical ratios were determined in comparison with authentic racemic material prepared using either triphenylphosphine or triphenylphosphite as the achiral ligand in the conjugate allylation reaction. Absolute stereochemistry was determined by subjecting the conjugate allylation product to ring-closing metathesis conditions using the Hoveyda-Grubbs' second generation catalyst, in CH_2Cl_2, to afford 5-phenyl-2-cycohexen-1-one (see page 358). The optical rotation was measured ($[\alpha]_D^{20}$ = +45° (*c* = 0.25, $CHCl_3$)) and compared to the known literature value.[78]

^{1}H NMR analysis of unpurified reaction mixture (400 MHz, $CDCl_3$):



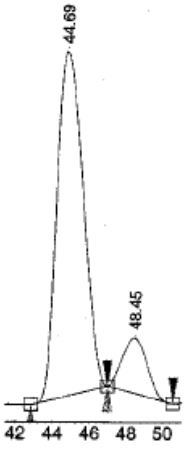
Vinyl CH
(minor + major
isomers)

*Chiral SFC (AS-H, Chiralpak, 150 bar, 50^{o}C, flow = 0.5 mL/min, 1.0 % MeOH) analysis of conjugate allylation product (**2.212**):*



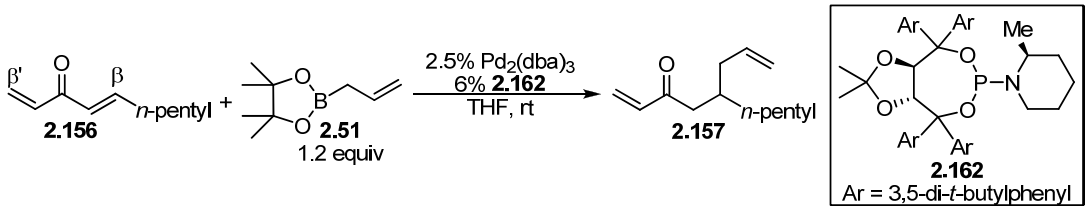
Allylation
product

Racemic



Allylation product
+ racemic
coinjection

Synthesis of 2.157

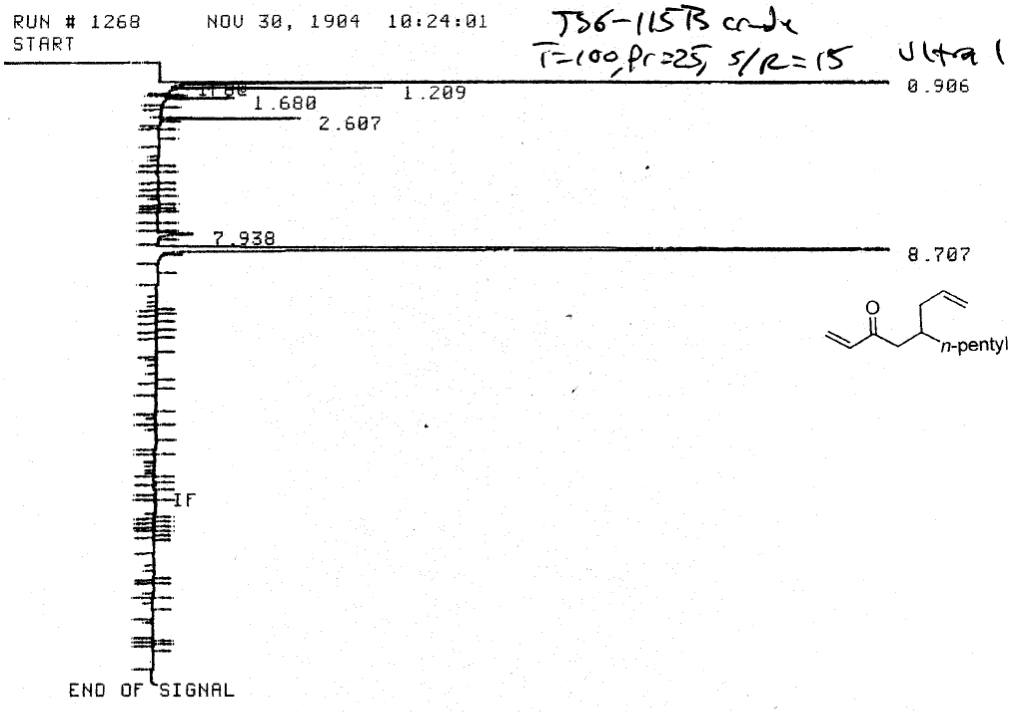


An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 3.0 mg (0.0033 mmol) of tris(dibenzylideneacetone)dipalladium(0), 8.2 mg (0.0079 mmol) of **2.162**, and 0.26 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 26.4 mg (0.157 mmol) of **2.51** and 20.0 mg (0.131 mmol) of **2.156** were added sequentially. The mixture was allowed to stir at ambient temperature for 14 h, and water was then added. The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried with anhydrous Na_2SO_4. Volatile material was removed under reduced pressure, and the mixture was purified using silica gel chromatography (hexanes/EtOAc). This afforded 13.2 mg (0.0679 mmol, 52%) of **2.157**. Achiral GLC of the unpurified mixture was used to determine the chemoselectivity of the reaction. The enantiomeric purity was measured using chiral GLC analysis of **2.157**. The absolute stereochemistry of **2.157** was not determined.

5-Allyldec-1-en-3-one (2.157). An oil. R_f = 0.26 (SiO_2, 30:1 hexanes:EtOAc); IR (neat): 3076 (m), 2958 (s), 2924 (s), 2848 (s), 1700 (s), 1683 (s), 1641 (m), 1611 (m), 1459 (m), 1396 (m), 1379 (m), 1299 (w), 1202 (w) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.31 (1H, dd, *J* = 18 Hz, *J* = 10 Hz), 6.16 (1H, d, *J* = 18 Hz), 5.76 (1H, d, *J* = 10 Hz), 5.64-5.80 (1H, m), 4.98 (1H, d, *J* = 12 Hz), 4.98 (1H, d, *J* = 16 Hz), 2.51 (1H, dd, *J* = 16 Hz, *J* =

6.4 Hz), 2.42 (1H, dd, *J* = 16 Hz, *J* = 6.0 Hz), 1.91-2.14 (3H, m), 1.12-1.36 (8H, m), 0.84 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 200.6, 136.9, 136.5, 127.6, 116.5, 44.00, 38.29, 33.84, 33.81, 32.01, 26.43, 22.61, 14.05. LRMS (ESI+) Calcd for $C_{13}H_{22}O$ $(M + H)^+$: 195.2, Found $(M + H)^+$: 195.2.

Achiral GLC (Ultra 1, Hewlett-Packard, 100 °C) analysis of unpurified reaction mixture:

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DIRECTORY FULL
Storing processed peaks to M:SIGNAL  .PRA

RUN#  1268          NOV 30, 1904  10:24:01

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   1.680       2058   BB   .024     .00402
   2.607       5165   PB   .031     .01008
   7.938       4436   BB   .104     .00866
   8.707     129519   PB   .120     .25276

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MUL FACTOR=1.0000E+00
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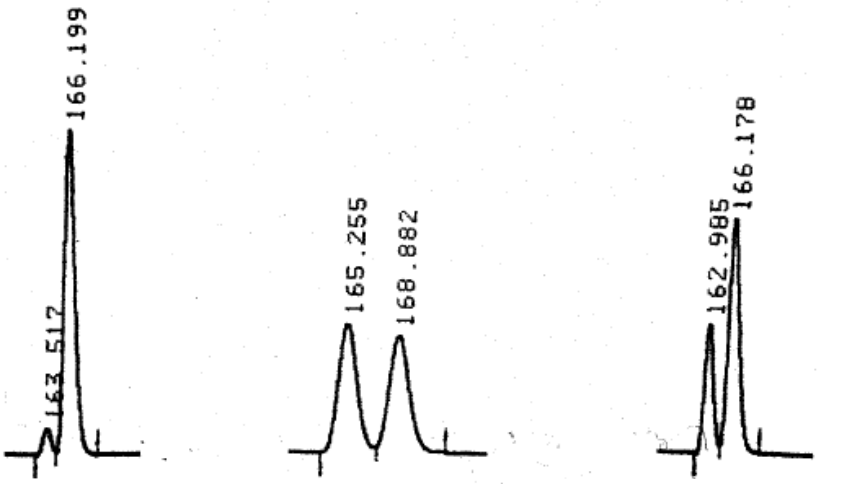
*Chiral GLC (β-dex, Supelco, 75°C) analysis of conjugate allylation product (**2.157**):*



conjugate allylation product

racemic

conjugate allylation product + racemic coinjection

```
js6-198column

exp1  std1h

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date    Feb 26 2008
solvent      CDCl3
file            exp
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tn               H1
at           3.000
np           35992
sw          5998.8
fb            3400
bs               4
tpwr            63
pw             7.1
d1           4.000
tof              0
nt               8
ct               8
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
     DISPLAY
sp            58.0
wp          2932.3
vs              32
sc               0
wc             250
hzmm         11.73
is         3185.51
rfl          3902.2
rfp          2896.2
th              20
ins          2.000
nm    ph

      DEC. & VT
dfrq             0
dn
dpwr            30
dof              0
dm             nnn
dmm              c
dmf            200
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proc            ft
fn        not used
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wexp
wbs
wnt
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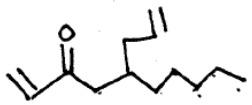
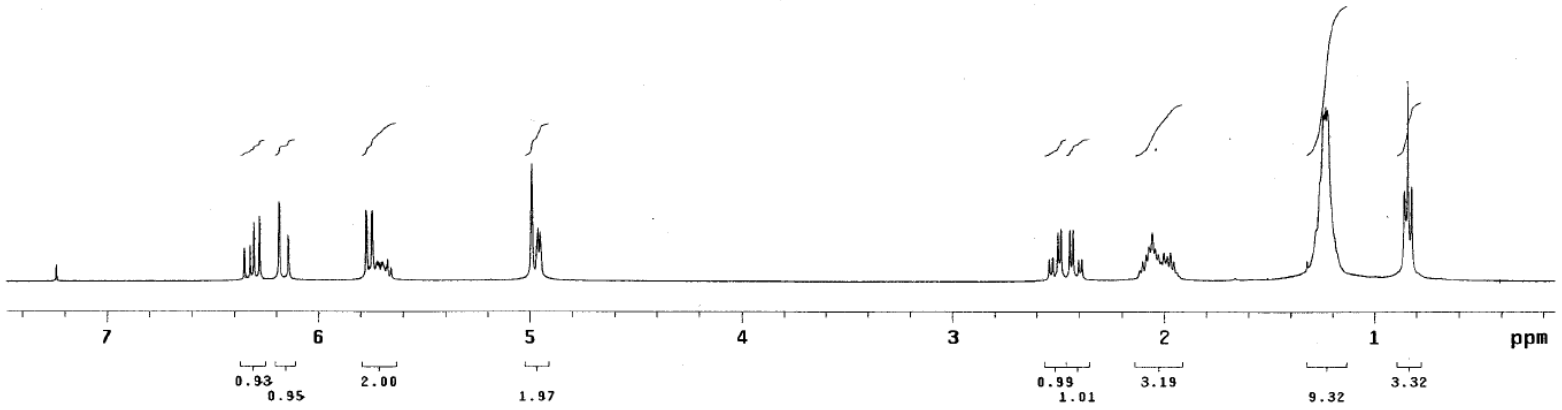
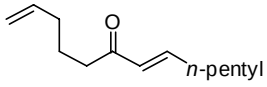
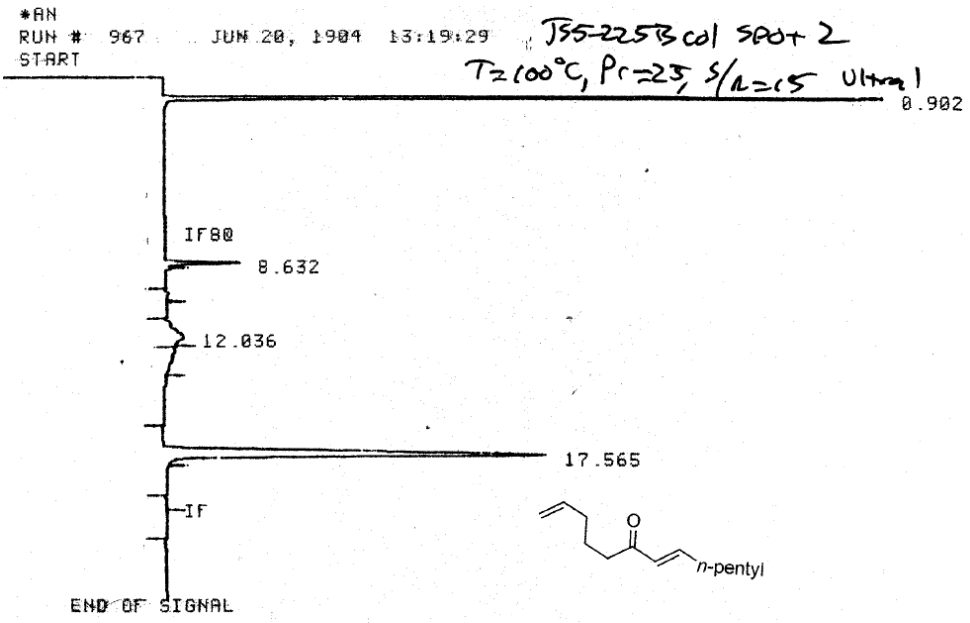






(*E*)-Trideca-1,7-dien-6-one (2.158). An oil. R_f = 0.18 (SiO_2, 30:1 hexanes:EtOAc); IR ($CDCl_3$ solution): 2966 (s), 2932 (s), 2856 (s), 1700 (s), 1675 (s), 1632 (s), 1455 (s), 1358 (m), 1253 (m), 1189 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.80 (1H, dt, *J* = 16 Hz, *J* = 7.0 Hz), 6.07 (1H, dt, *J* = 16 Hz, *J* = 1.5 Hz), 5.76 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 7.0 Hz), 5.00 (1H, dq, *J* = 17 Hz, *J* = 1.5 Hz), 4.93-4.97 (1H, m), 2.52 (2H, t, *J* = 7.5 Hz), 2.18 (2H, q, *J* = 7.0 Hz), 2.06 (2H, q, *J* = 7.0 Hz), 1.70 (2H, p, *J* = 7.0 Hz), 1.44 (2H, p, *J* = 7.5 Hz), 1.21-1.35 (4H, m), 0.87 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 200.6, 147.6, 138.1, 130.3, 115.1, 39.15, 33.17, 32.40, 31.34, 27.77, 23.27, 22.41, 13.95. LRMS (ESI+) Calcd for $C_{13}H_{22}O$ $(M + H)^+$: 195.2, Found $(M + H)^+$: 195.2.

*Achiral GLC (Ultra 1, Hewlett-Packard, 100 ^{o}C) analysis of **2.158**:*

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DIRECTORY FULL
Storing processed peaks to M:SIGNAL   .PRA

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  17.565     129064   PB    .279     .72379

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MUL FACTOR=1.0000E+00
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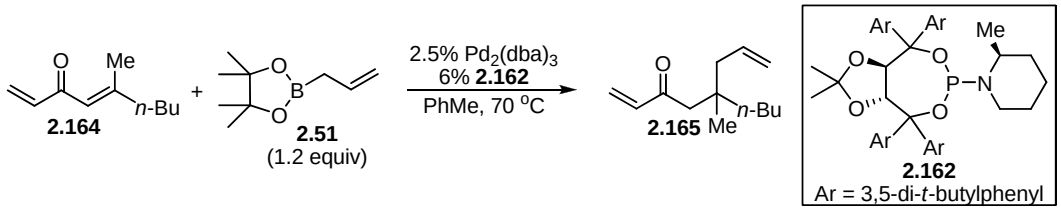
Representative procedure for asymmetric allylation of 2.164:

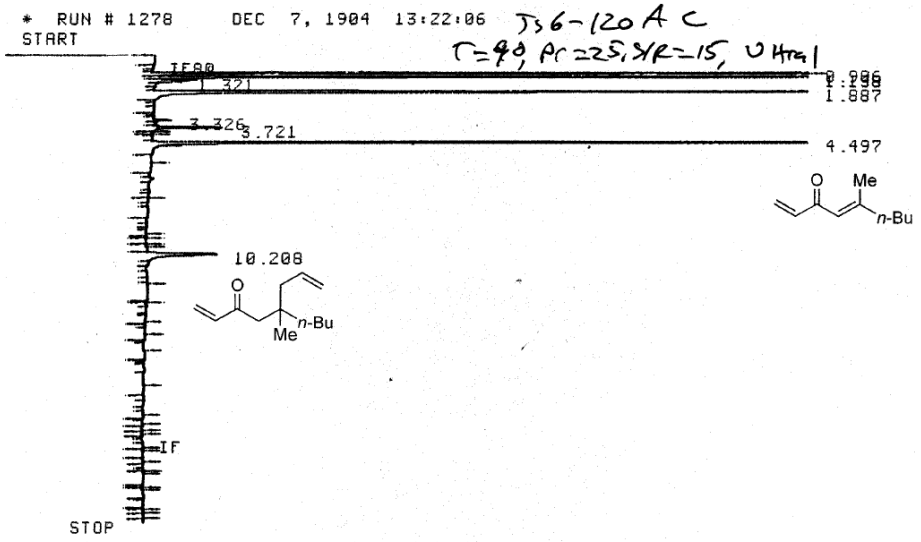


An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 3.0 mg (0.0033 mmol) of tris(dibenzylideneacetone)dipalladium(0), 8.2 mg (0.0079 mmol) of **2.162**, and 0.66 mL of toluene in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 26.4 mg (0.157 mmol) of **2.51** and 20.0 mg (0.131 mmol) of **2.164** were added sequentially. The vial was capped, sealed with electrical tape, removed from the dry-box, and heated at 70 ^{o}C for 18 h. Degassed water (N_2 sparge) was then added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. Conversion and chemoselectivity were determined by achiral GLC analysis of the unpurified reaction mixture. Stereochemical ratios were determined on purified material using chiral GLC analysis of **2.165**. Racemic **2.165** was prepared by conducting the conjugate allylation with 5% $Ni(cod)_2$ and 10% racemic **2.114** as ligand. This gave a 1.35:1 mixture of constitutional isomers favoring **2.165** in 36% combined yield. Separation was achieved using silica gel chromatography (hexanes/EtOAc). The absolute stereochemistry of **2.165** was not determined.

5-Allyl-5-methylnon-1-en-3-one (2.165). An oil. R_f = 0.24 (SiO_2, 40:1 hexanes:EtOAc); ^{1}H NMR ($CDCl_3$): δ 6.33 (1H, dd, *J* = 18 Hz, *J* = 10 Hz), 6.14 (1H, d,

J = 18 Hz), 5.70-5.84 (1H, m), 5.70 (1H, d, *J* = 10 Hz), 4.86-5.07 (2H, m), 2.43 (2H, s), 2.02-2.18 (2H, m), 1.14-1.36 (6H, m), 0.95 (3H, s), 0.87 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 200.4, 138.0, 134.9, 127.1, 117.5, 47.98, 44.00, 39.39, 36.66, 36.11, 25.96, 25.06, 14.15. LRMS (ESI+) Calcd for $C_{13}H_{22}O$ $(M + H)^+$: 195.2, Found $(M + H)^+$: 195.2.

Achiral GLC (Ultra 1, Hewlett-Packard, 90 °C) analysis of unpurified reaction mixture:



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RUN# 1278 DEC 7, 1904 13:22:06

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3.326	807	VV	.061	.00596
3.721	2668	VB	.058	.01972
4.497	41768	PB	.053	.30869
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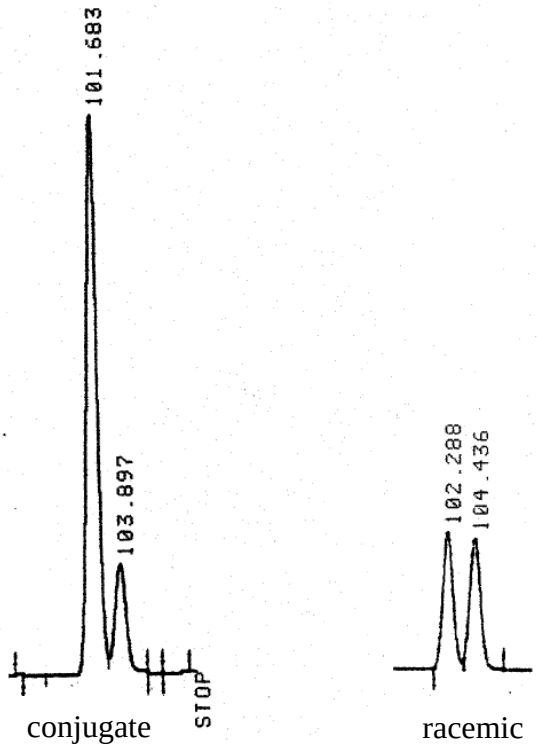
14% conv.

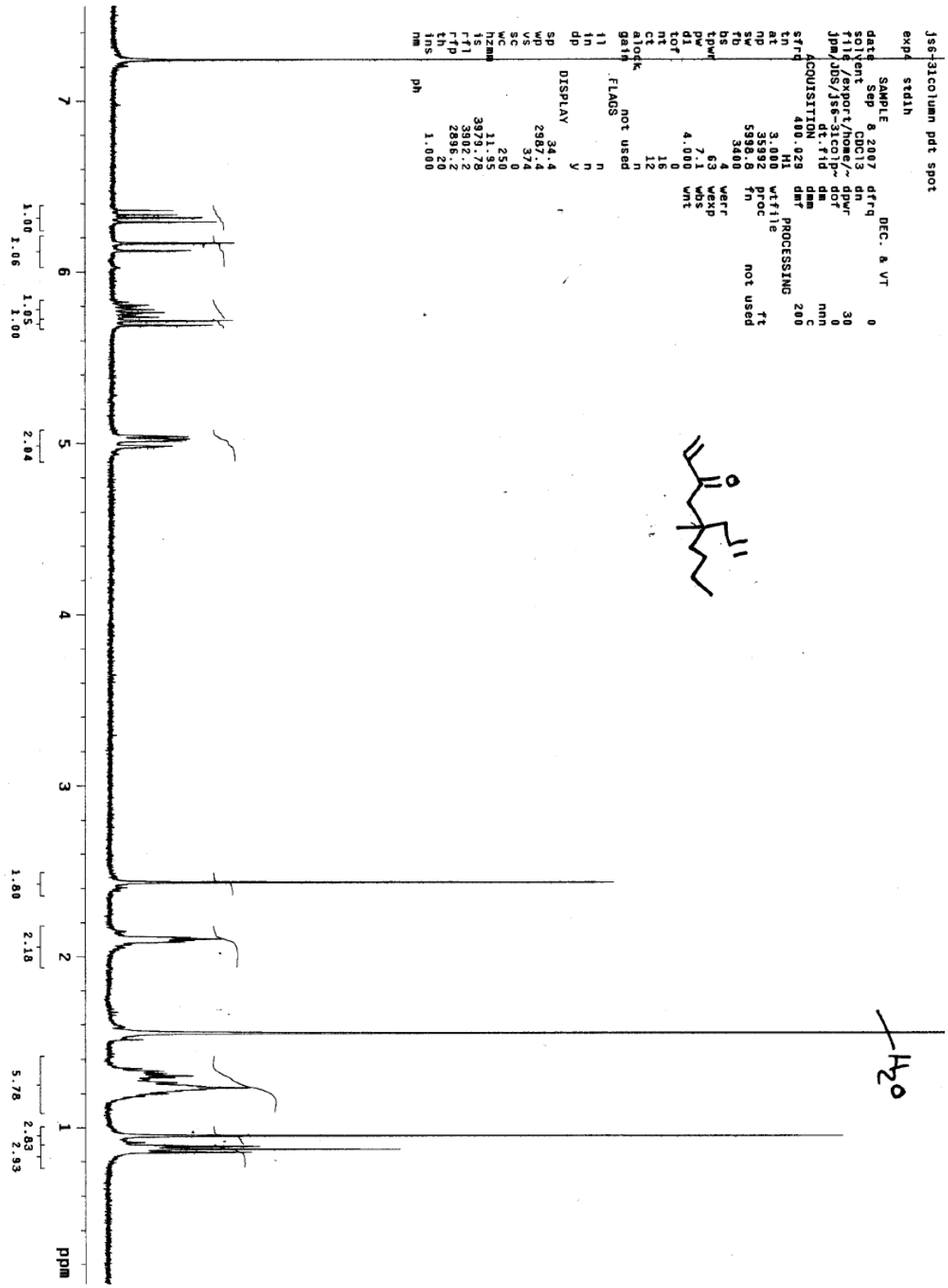
TOTAL AREA=1.3531E+07
MUL FACTOR=1.0000E+00

*Chiral GLC (β-dex, Supelco, 75°C) analysis of conjugate allylation product (**2.165**):*



conjugate allylation product

racemic


js6-3icolumn pdt spot
exp4 stdin
SAMPLE
date Sep 8 2007
solvent CDCl3
file /export/home/~
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at 3.000
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sw 5998.8
fb 3400
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ct 12
alock n
gain n
FLAGS
il n
in n
dp y
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wp 2987.4
vs 374
sc 0
wc 250
hzmm 11.95
is 3979.78
rfl 3902.2
rfp 2896.2
th 20
ins 1.000
ph
DEC. & VT
dfrq 0
dn
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
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ft
proc
fn not used
wexp
wbs
wnt
not used
H2O
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1.06
1.05
1.00
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2.93
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5
4
3
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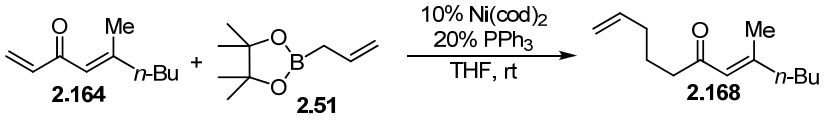
1
ppm

Synthesis of 2.168

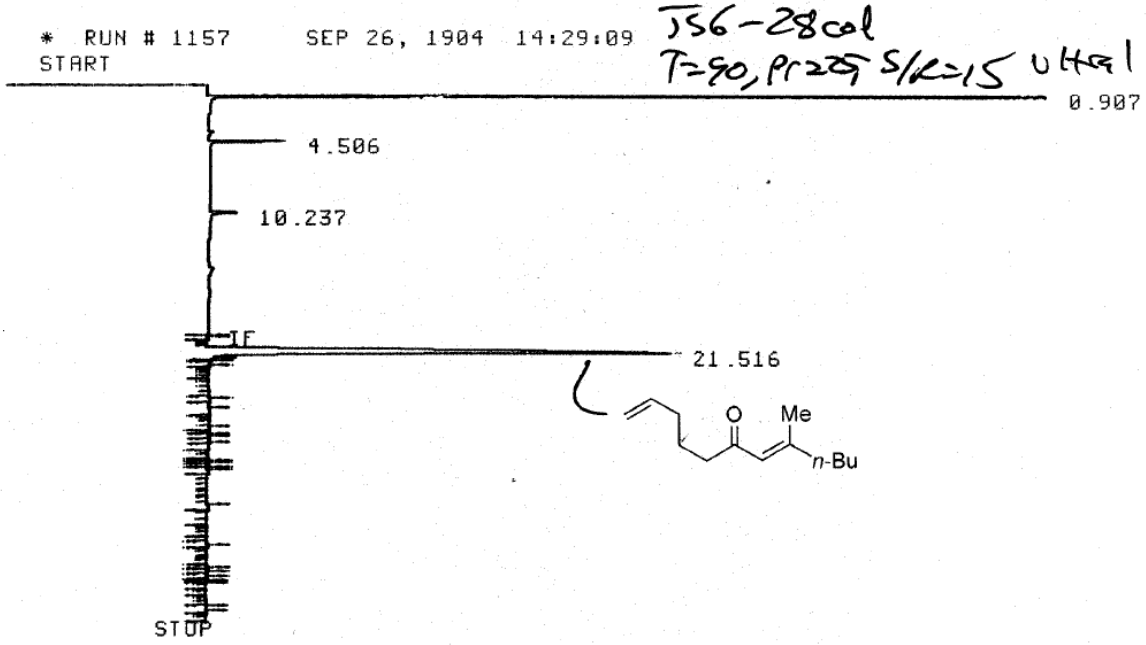


An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 4.5 mg (0.016 mmol) of bis(1,5-cyclooctadiene)nickel(0), 8.6 mg (0.033 mmol) of triphenylphosphine, and 0.82 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 5 min. Next, 33.1 mg (0.197 mmol) of **2.51** and 25.0 mg (0.164 mmol) of **2.164** were added sequentially. The vial was capped, taped with electrical tape, removed from the dry-box, and heated at 70 ^{o}C for 26 h. Degassed water (N_2 sparge) was then added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. Conversion and chemoselectivity was determined by achiral GLC analysis of the unpurified reaction mixture. Purification of the mixture using silica gel chromatography (hexanes/EtOAc) afforded 9.7 mg (0.050 mmol, 30%) of **2.168**.

(*E*)-8-Methyldodeca-1,7-dien-6-one (2.168). An oil. R_f = 0.20 (SiO_2, 40:1 hexanes:EtOAc); IR (neat): 3080 (m), 2958 (s), 2932 (s), 2860 (s), 1691 (s), 1620 (s), 1464 (m), 1442 (m), 1413 (m), 1362 (m), 1223 (w), 1130 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.02 (1H, s), 5.77 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 6.4 Hz), 4.90-5.04 (2H, m), 2.40 (2H, t, *J* = 7.2 Hz), 2.00-2.14 (7H, m), 1.67 (2H, p, *J* = 7.6 Hz), 1.36-1.48 (2H, m), 1.29 (2H, h, *J* = 7.2 Hz), 0.89 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 201.0, 158.6, 138.2,

123.0, 114.9, 43.57, 40.96, 33.25, 29.72, 23.43, 22.39, 19.30, 13.90. LRMS (ESI+) Calcd for $C_{13}H_{22}O$ $(M + H)^+$: 195.2, Found $(M + H)^+$: 195.2.

*Achiral GLC (Ultra 1, Hewlett-Packard, 90 °C) analysis of **2.168**:*

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   4.506       5298   PB    .066     .04406
  10.237       4311   VV    .140     .03585
  21.516     164988   PB    .348    1.37195

TOTAL AREA=1.2026E+07
MUL FACTOR=1.0000E+00
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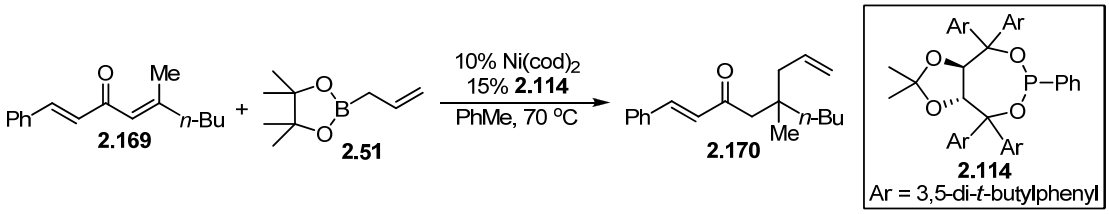
Synthesis of 2.170



An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 4.2 mg (0.015 mmol) of bis(1,5-cyclooctadiene)nickel(0), 23.5 mg (0.0230 mmol) of **2.114**, and 0.50 mL of toluene in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 30.9 mg (0.184 mmol) of **2.51** and 35.0 mg (0.153 mmol) of **2.169** were added sequentially. The vial was capped, sealed with electrical tape, removed from the dry-box, and heated at 70 ^{o}C for 20 h. The reaction was quenched by the addition of unpurified, degassed (N_2 sparge) MeOH. Water was then added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. Chemoselectivity was determined by achiral GLC analysis of the unpurified reaction mixture.[1] Purification of the mixture using silica gel chromatography (hexanes/EtOAc) afforded 8.7 mg (0.032 mmol, 21%) of **2.170** contaminated with some of the other constitutional isomer derived from benzylidene conjugate allylation. Stereochemical ratios were determined using chiral SFC analysis of the alcohol obtained from 1,2-

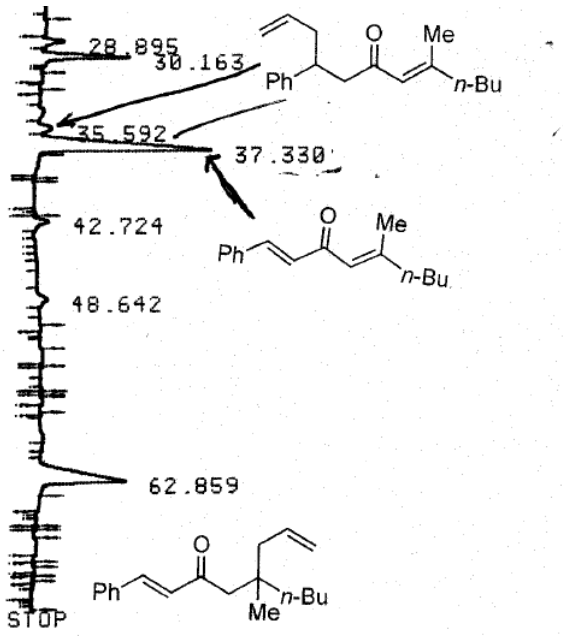
[1] The minor constitutional isomer was prepared by another route to obtain a GLC standard. This synthesis is given on page 303.

reduction of **2.170** using LAH at -78 ^{o}C in THF.[2] The absolute configuration of **2.170** was not determined.

(*E*)-5-Allyl-5-methyl-1-phenylnon-1-en-3-one (2.170). An oil. R_f = 0.17 (SiO_2, 25:1 hexanes:EtOAc); IR ($CDCl_3$ solution): 3067 (w), 3025 (w), 2962 (s), 2932 (s), 2860 (m), 1687 (s), 1649 (s), 1603 (s), 1573 (m), 1497 (m), 1451 (s), 1371 (m), 1328 (m), 1198 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.49-7.56 (2H, m), 7.48 (1H, d, *J* = 16 Hz), 7.34-7.40 (3H, m), 6.72 (1H, d, *J* = 16 Hz), 5.81 (1H, ddt, *J* = 17 Hz, *J* = 11 Hz, *J* = 7.5 Hz), 4.98-5.09 (2H, m) 2.52 (2H, s), 2.08-2.20 (2H, m), 1.30-1.43 (2H, m), 1.18-1.30 (4H, m), 1.00 (3H, s), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 200.1, 141.7, 135.0, 134.6, 130.3, 128.9, 128.3, 127.6, 117.6, 49.54, 44.04, 39.40, 36.92, 25.94, 25.11, 23.40, 14.16. LRMS (ESI+) Calcd for $C_{19}H_{26}O$ $(M + H)^+$: 271.2, Found $(M + H)^+$: 271.2.

[2] The reduction product existed as a ~1:1 mixture of diastereomers that were inseparable by column chromatography on silica gel [R_f = 0.28 (9:1 hexanes:EtOAc)].

Achiral GLC (Ultra 1, Hewlett-Packard, 135 ^{o}C) analysis of unpurified reaction mixture:

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DIRECTORY FULL

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  24.061       6625   VV    .442     .01369
  28.895       7556   BV    .352     .01562
  30.163      31959   VV    .365     .06605
  35.592       7524   PV    .523     .01555
  37.330     111549   VB    .646     .23055
  42.724       5680   PP    .398     .01174
  48.642       5801   PV    .586     .01199
  62.859      80061   VB    .927     .16547

TOTAL AREA=4.8383E+07
MUL FACTOR=1.0000E+00
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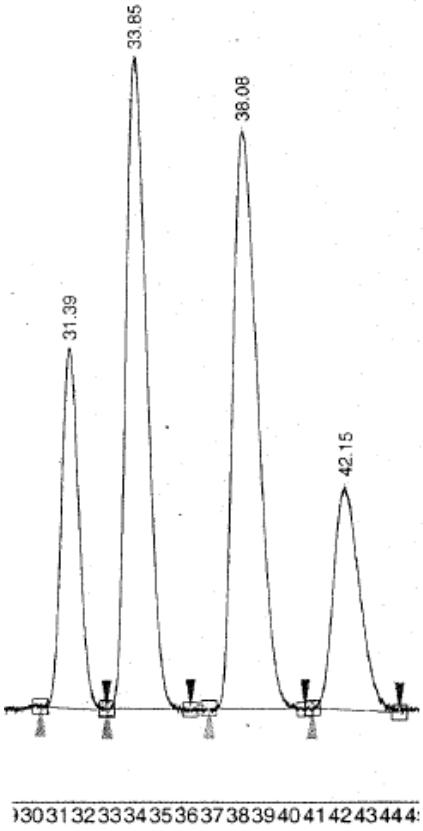
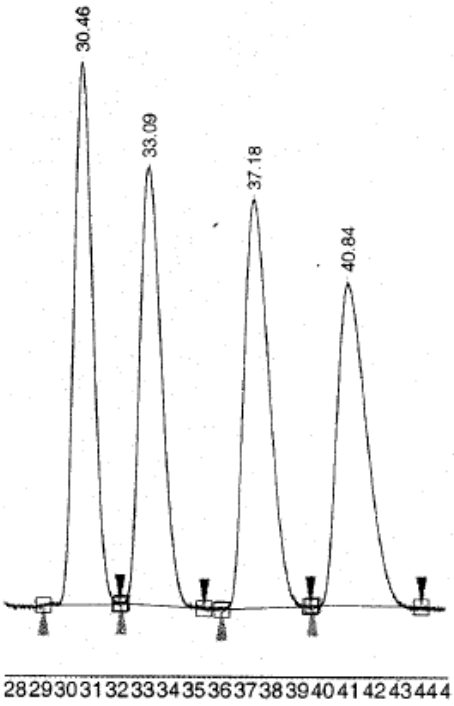
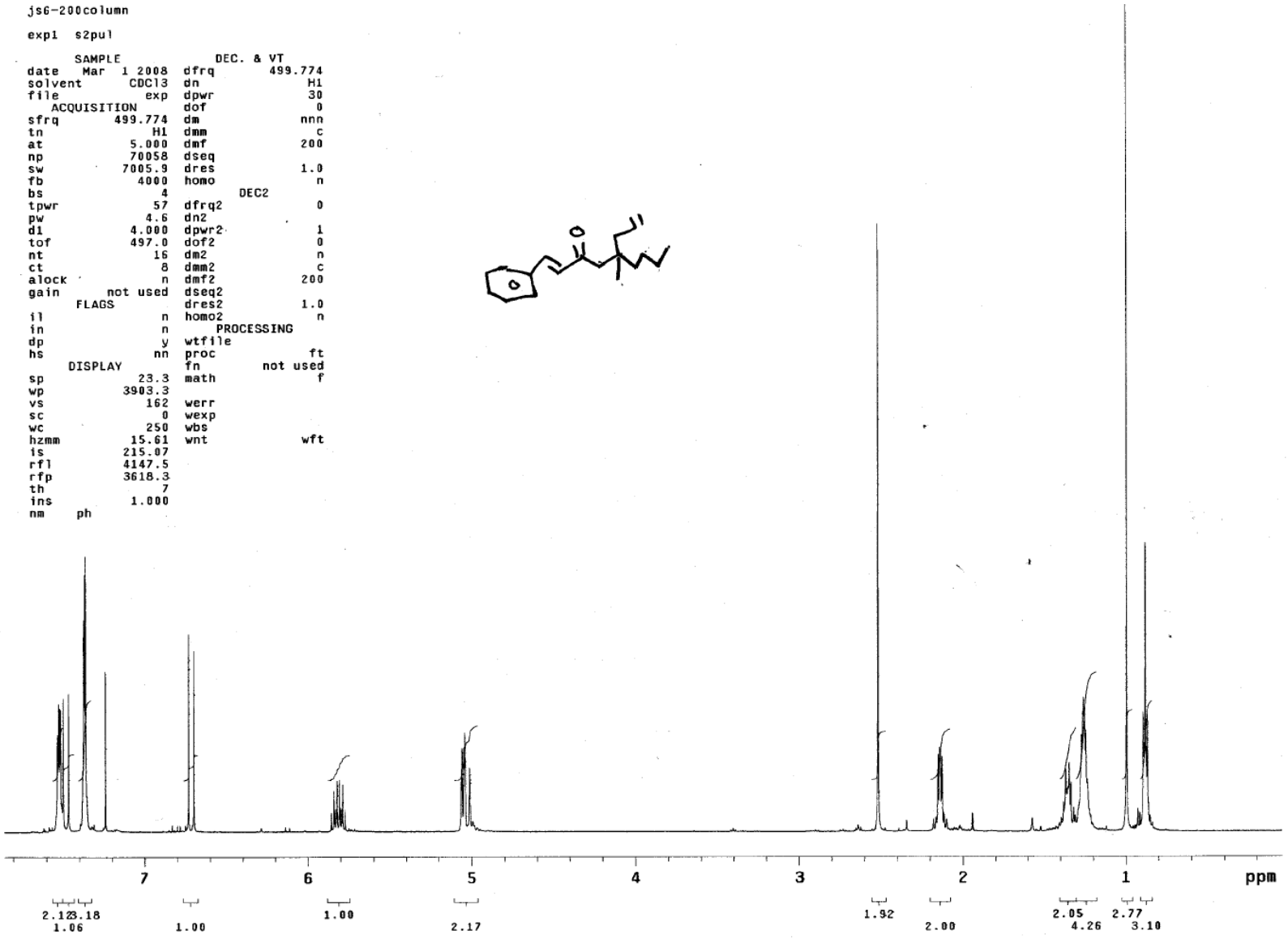
*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 1.0 mL/min, 2.0 % MeOH) analysis of the alcohol from reduction of **2.170** with LAH at -78 °C:*



conjugate allylation-reduction product



racemic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exp1 s2pul
SAMPLE
date Mar 1 2008
solvent CDCl3
file exp
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at 5.000
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sw 7005.9
fb 4000
bs 4
tpwr 57
pw 4.6
d1 4.000
tof 497.0
nt 16
ct 8
alock n
gain not used
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in n
dp y
hs nn
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wp 3903.3
vs 162
sc 0
wc 250
hzmm 15.61
is 215.07
rfl 4147.5
rfp 3618.3
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nm ph
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dseq
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dres2 1.0
homo2 n
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math f
werr
wexp
wbs
wnt wft
7
6
5
4
3
2
1
ppm
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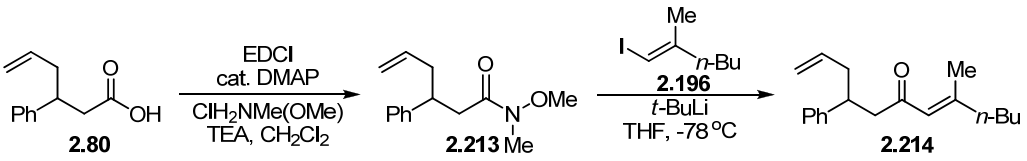
2.00
2.05
4.26
2.77
3.10

Synthesis of 2.214



To 28.1 mg (0.148 mmol) of **2.80** (see page 360) and 21.7 mg (0.222 mmol) of (*N*,*O*)-dimethylhydroxylamine hydrochloride in 0.60 mL of CH_2Cl_2 in a 2-dram vial with magnetic stir-bar was added 3.6 mg (0.030 mmol) of 4-(dimethylamino)pyridine (DMAP) followed by 42.6 mg (0.222 mmol) of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI), all in one portion. This mixture was put under N_2, and 0.03 mL (0.2 mmol) of triethylamine was added. The mixture was then allowed to stir for 3 h. The final mixture was transferred to a separatory funnel, washed with 3 M HCl (2x) followed by saturated aqueous $NaHCO_3$. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Silica gel chromatography (hexanes:EtOAc) afforded 26.8 mg (0.115 mmol, 78%) of Weinreb amide **2.213**.

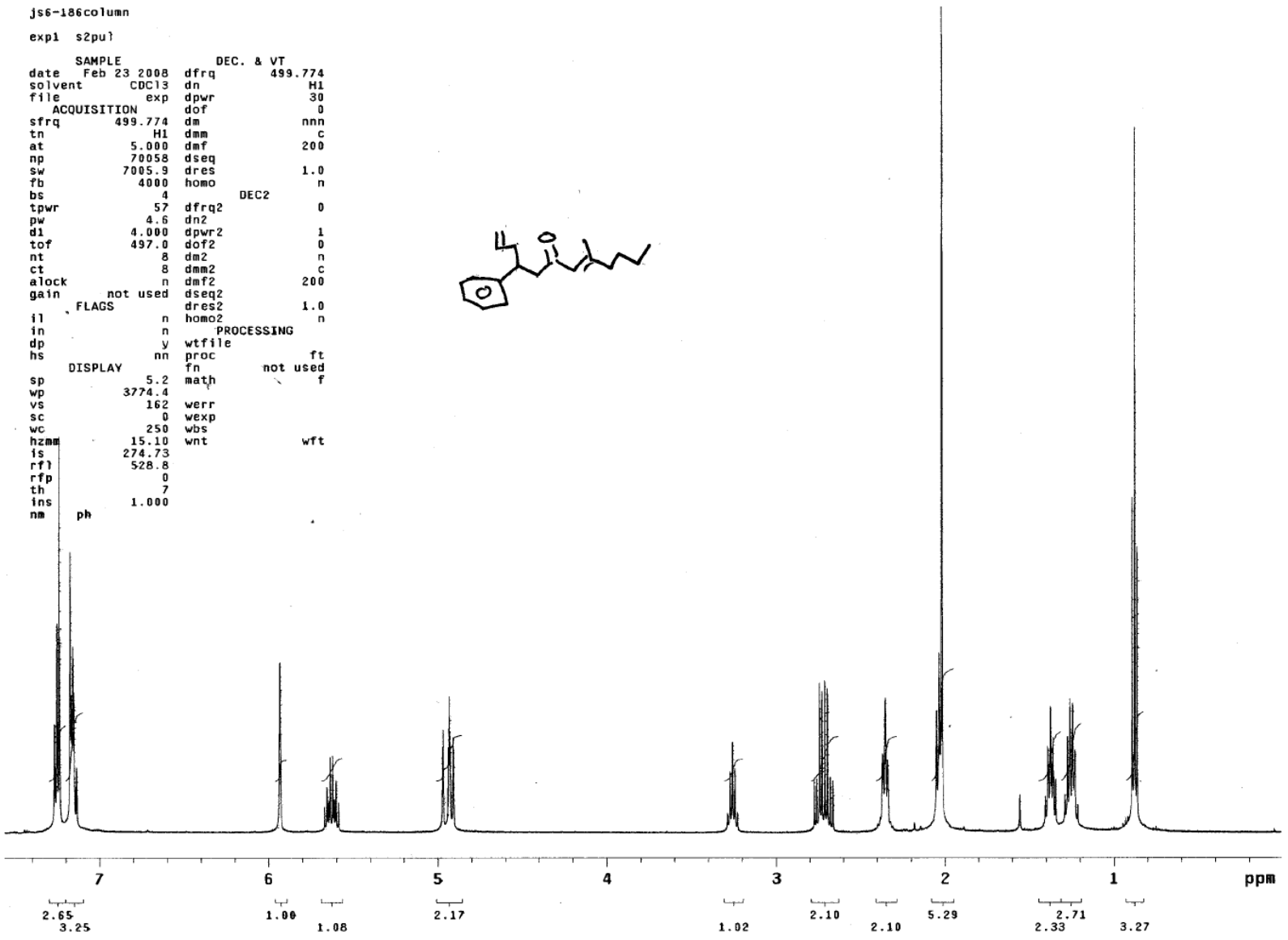
To 48.2 mg (0.215 mmol) of **2.196** in 0.50 mL of THF at –78 ^oC was added 0.33 mL (0.43 mmol) of a 1.3 M solution of *t*-BuLi in pentane dropwise. This solution was allowed to stir at this temperature for 30 min and then transferred by canula to a solution of 22.8 mg (0.0977) of **2.213** (dried by azeotropic removal of water with benzene) in 0.90 mL of THF at –78 ^oC. After complete addition (5 min), the reaction was allowed to stir for 1 h at –78 ^oC. To the mixture was then added 0.2 mL of MeOH, the dry-ice acetone bath was removed, and water was added. After reaching room temperature, the mixture was transferred to a separatory funnel with water and Et_2O. The organic layer was

collected after shaking, and the aqueous layer was extracted with Et_2O (1x). The combined organics were washed with saturated aqueous $NaHCO_3$ and dried with anhydrous Na_2SO_4. Volatile material was removed under reduced pressure, and purification of the mixture using silica gel chromatography (hexanes/EtOAc) afforded 13.8 mg (0.0510 mmol, 52%, 79% brsm) of **2.214** along with 7.7 mg of unreacted **2.213**.

***N*-Methoxy-*N*-methyl-3-phenylhex-5-enamide (2.213).** An oil. R_f = 0.27 (SiO_2, 2:1 hexanes:EtOAc); IR ($CDCl_3$ solution): 3392 (br, s), 3067 (m), 3029 (m), 2932 (s), 2852 (m), 1945 (w), 1729 (m), 1661 (s), 1493 (m), 1455 (s), 1421 (s), 1383 (s), 1180 (m), 1117 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.10-7.40 (5H, m), 5.65 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 6.8 Hz), 4.97 (1H, d, *J* = 17 Hz), 4.93 (1H, d, *J* = 10 Hz), 3.53 (3H, s), 3.31 (1H, p, *J* = 7.6 Hz), 3.08 (3H, s), 2.72 (2H, d, *J* = 6.8 Hz), 2.30-2.50 (2H, m); ^{13}C NMR ($CDCl_3$): δ 181.2, 144.3, 136.3, 128.2, 127.5, 126.2, 116.4, 61.11, 41.13, 40.41, 38.07, 29.68. LRMS (ESI+) Calcd for $C_{14}H_{19}NO_2$ $(M + H)^+$: 234.2, Found $(M + H)^+$: 234.2.

(*E*)-8-Allyl-5-methyl-1-phenylnon-1-en-3-one (2.214). An oil. R_f = 0.15 (SiO_2, 30:1 hexanes:EtOAc); IR ($CDCl_3$ solution): 3076 (w), 3029 (w), 2958 (s), 2928 (s), 2864 (m), 1683 (s), 1619 (s), 1493 (m), 1451 (m), 1383 (m), 1227 (w), 1130 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.20-7.30 (2H, m), 7.12-7.20 (3H, m), 5.93 (1H, q, *J* = 1.0 Hz), 5.63 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 7.0 Hz), 4.89-5.00 (2H, m), 3.26 (1H, p, *J* = 7.0 Hz), 2.74 (1H, dd, *J* = 15 Hz, *J* = 6.5 Hz), 2.69 (1H, dd, *J* = 15 Hz, *J* = 7.5 Hz), 2.35 (2H, t, *J* = 8.0 Hz), 2.04 (2H, t, *J* = 7.5 Hz), 2.02 (3H, s), 1.32-1.42 (2H, m), 1.25 (2H, h, *J* = 8.0 Hz), 0.88

(3H, t, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$): δ 199.8, 159.0, 144.4, 136.4, 128.3, 127.5, 126.2, 123.4, 116.5, 50.21, 41.07, 40.84, 40.76, 29.56, 22.30, 19.27, 13.89. LRMS (ESI+) Calcd for $C_{19}H_{26}O$ $(M + H)^+$: 271.2, Found $(M + H)^+$: 271.2.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pw 4.6
d1 4.000
tof 497.0
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ct 8
alock n
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in n
dp y
hs nn
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dmm c
dmf 200
dseq
dres 1.0
homo n
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dm2 n
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dres2 1.0
homo2 n
PROCESSING
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ppm
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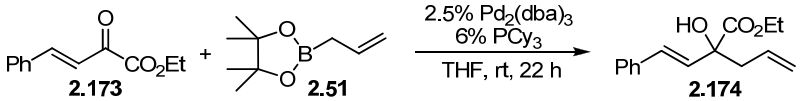
Synthesis of 2.174

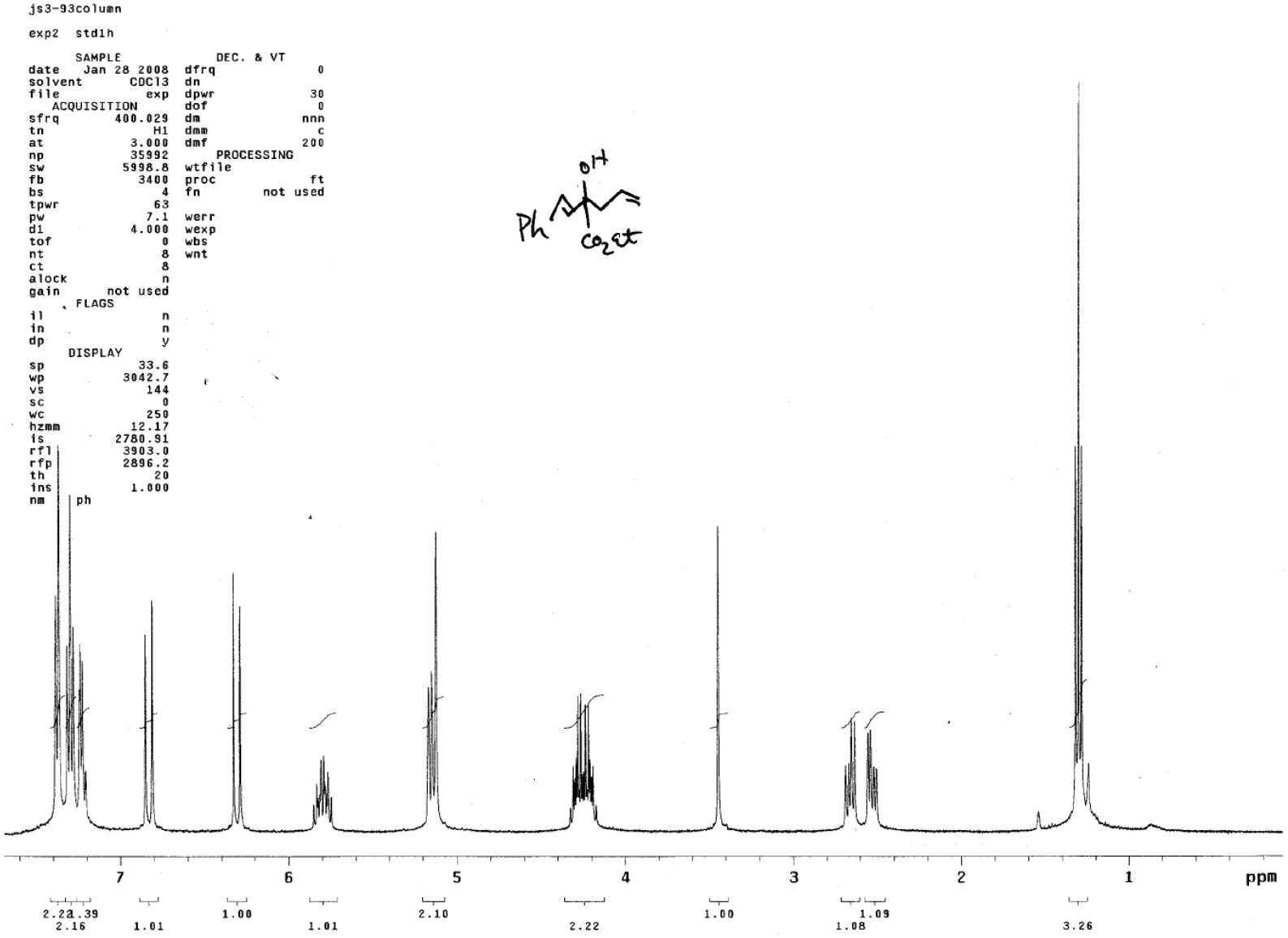


An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 2.3 mg (0.0025 mmol) of tris(dibenzylideneacetone)dipalladium(0), 1.7 mg (0.0060 mmol) of tricyclohexylphosphine, and 0.20 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 25 mg (0.15 mmol) of **2.51** and 0.15 mL (0.10 mmol) of a 0.68 M solution of **2.173**[1] in THF were added sequentially. The mixture was allowed to stir at ambient temperature for 22 h, and water was then added. The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried with anhydrous Na_2SO_4. Volatile material was removed under reduced pressure, and the mixture was purified using silica gel chromatography (hexanes/EtOAc). This afforded 23.5 mg (0.0954 mmol, 94%) of **2.174**.

(*E*)-Ethyl 2-hydroxy-2-styrylpent-4-enoate (2.174). An oil. R_f = 0.21 (SiO_2, 8:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3510 (br, s), 3080 (m), 3025 (m), 2983 (m), 2920 (m), 1966 (w), 1734 (s), 1645 (m), 1451 (m), 1366 (m), 1286 (m), 1223 (s), 1160 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.38 (2H, d, *J* = 7.2 Hz), 7.30 (2H, t, *J* = 7.2 Hz), 7.18-7.25 (1H, m), 6.83 (1H, d, *J* = 16 Hz), 6.31 (1H, d, *J* = 16 Hz), 5.80 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 7.2 Hz), 5.14 (1H, d, *J* = 17 Hz), 5.13 (1H, d, *J* = 10 Hz), 4.15-4.35 (2H, m), 3.45 (1H, s), 2.66 (1H, dd, *J* = 14 Hz, *J* = 8.0 Hz), 2.53 (1H, dd, *J* = 14 Hz, *J* = 6.8 Hz),

[1] Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635.

1.30 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 174.4, 136.4, 132.0, 130.1, 129.6, 128.5, 127.8, 126.7, 119.2, 77.02, 62.39, 44.03, 14.28. LRMS (ESI+) Calcd for $C_{15}H_{18}O_3$ $(M + NH_4)^+$: 264.2, Found $(M + NH_4)^+$: 264.2.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SAMPLE
date Jan 28 2008
solvent CDCl3
file exp
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at 3.000
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sw 5998.8
fb 3400
bs 4
tpwr 63
pw 7.1
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tof 0
nt 8
ct 8
alock n
gain not used
FLAGS
il n
in n
dp y
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wp 3042.7
vs 144
sc 0
wc 250
hzmm 12.17
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rfl 3903.0
rfp 2896.2
th 20
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nm ph
DEC. & VT
dfrq 0
dn
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
Ph
OH
CO2Et
7
6
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3
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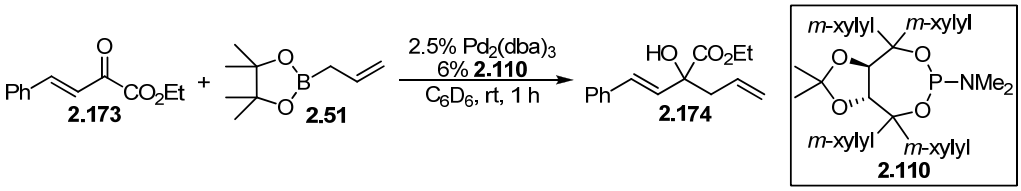
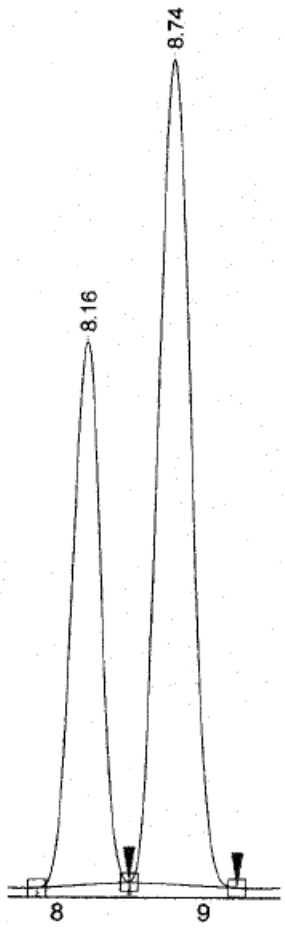
1.00
1.09
1.08
3.26

Asymmetric Synthesis of 2.174

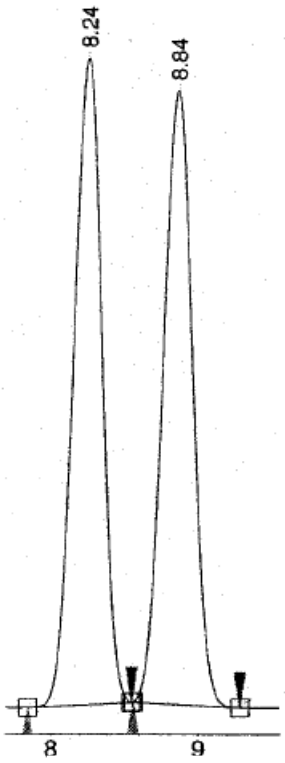


An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 2.3 mg (0.0025 mmol) of tris(dibenzylideneacetone)dipalladium(0), 3.9 mg (0.0060 mmol) of **2.110**, and 0.20 mL of C_6D_6 in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 25 mg (0.15 mmol) of **2.51** and 0.15 mL (0.10 mmol) of a 0.68 M solution of **2.173** in C_6D_6 were added sequentially. The mixture was transferred to an NMR tube and monitored by NMR. After 1 h, water was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. The residue was purified using silica gel chromatography (hexanes/EtOAc). This afforded 14 mg (0.057 mmol, 56%) of **2.174** that was determined to have an enantiomeric purity of 27% ee by analysis of **2.174** using chiral SFC. The absolute configuration was not determined.

*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 1.0 mL/min, 4.0 % MeOH) analysis of **2.174**:*

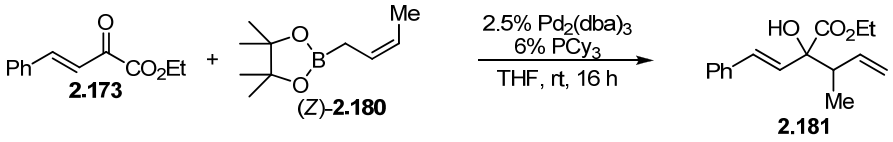


allylation product



racemic

Synthesis of 2.181

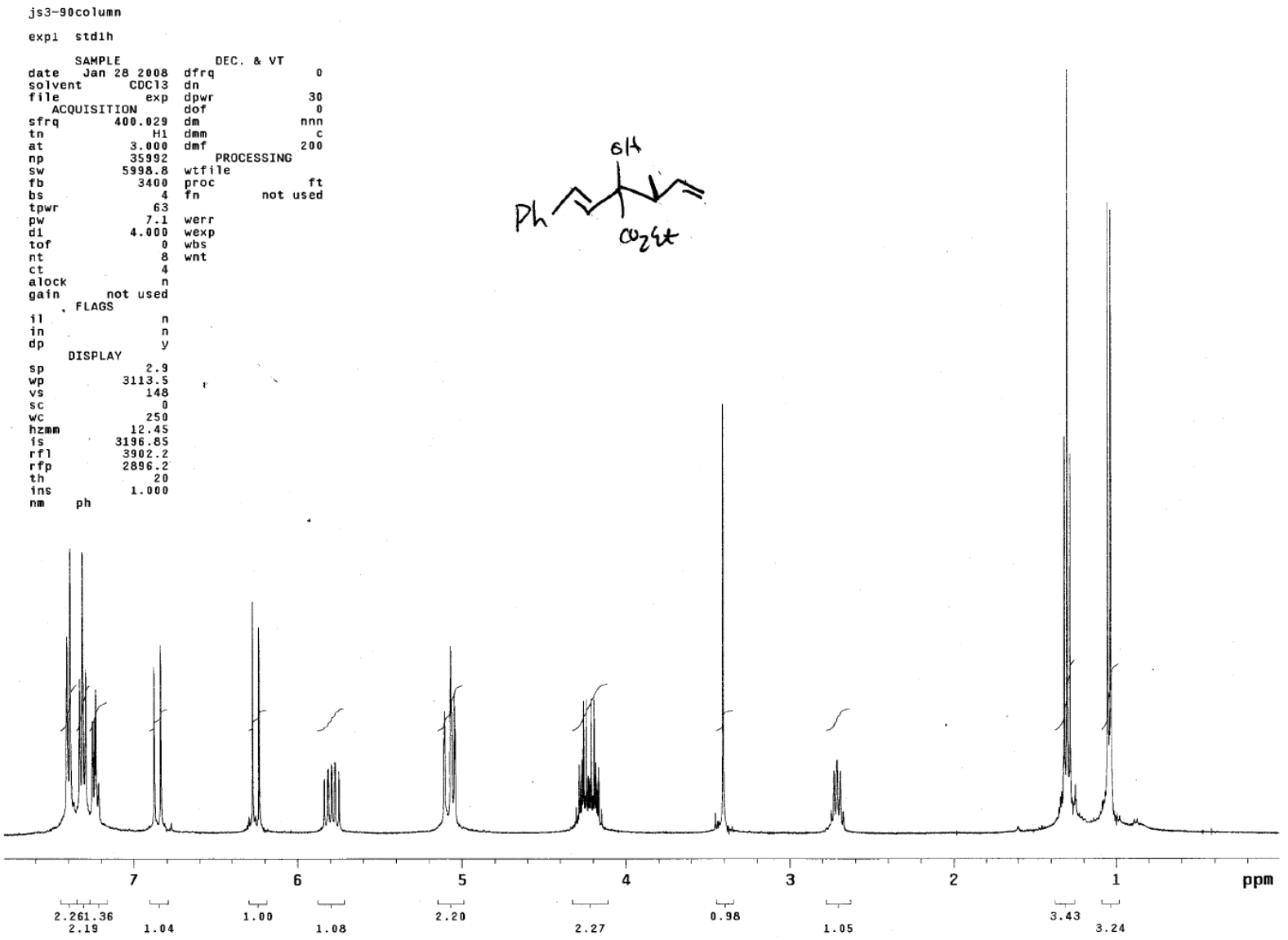


An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 2.3 mg (0.0025 mmol) of tris(dibenzylideneacetone)dipalladium(0), 1.7 mg (0.0060 mmol) of tricyclohexylphosphine, and 0.20 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 0.40 mL of THF, 27 mg (0.15 mmol) of (*Z*)-**2.180**,[1] and 0.15 mL (0.10 mmol) of a 0.68 M solution of **2.173** in THF were added sequentially. The mixture was allowed to stir at ambient temperature for 16 h, and water was then added. The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried with anhydrous Na_2SO_4. Volatile material was removed under reduced pressure, and the mixture was purified using silica gel chromatography (hexanes/EtOAc). This afforded 24.1 mg (0.0926 mmol, 93%) of **2.181** as a single diastereomer by ^{1}H NMR analysis. The relative stereochemistry was not determined.

(*E*)-Ethyl 2-hydroxy-3-methyl-2-styrylpent-4-enoate (2.181). An oil. R_f = 0.32 (SiO_2, 8:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3510 (br, s), 3080 (m), 3025 (m), 2979 (s), 2936 (m), 2869 (m), 1953 (w), 1877 (w), 1725 (s), 1637 (m), 1497 (m), 1447 (m), 1371 (m), 1295 (m), 1244 (s), 1142 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.35-7.47 (2H, m), 7.31

[1] Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.

(2H, t, *J* = 7.2 Hz), 7.18-7.26 (1H, m), 6.86 (1H, d, *J* = 16 Hz), 6.25 (1H, d, *J* = 16 Hz), 5.79 (1H, ddd, *J* = 17 Hz, *J* = 10 Hz, *J* = 8.4 Hz), 5.00-5.15 (2H, m), 4.14-4.34 (2H, m), 3.40 (1H, s), 2.71 (1H, p, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.04 (3H, d, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 174.7, 138.6, 136.5, 130.7, 129.0, 128.5, 127.6, 126.6, 116.3, 79.65, 62.34, 45.77, 14.25, 13.74. LRMS (ESI+) Calcd for $C_{16}H_{20}O_3$ $(M - H_2O + H)^+$: 243.1, Found $(M - H_2O + H)^+$: 243.1.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date Jan 28 2008
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sw 5998.8
fb 3400
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pw 7.1
d1 4.000
tof 0
nt 8
ct 4
alock n
gain not used
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il n
in n
dp y
DISPLAY
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wp 3113.5
vs 148
sc 0
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hzmm 12.45
is 3196.85
rfl 3902.2
rfp 2896.2
th 20
ins 1.000
nm ph
DEC. & VT
dfrq 0
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dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
Ph
CO2Et
7
6
5
4
3
2
1
ppm
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1.00
1.08
2.20
2.27
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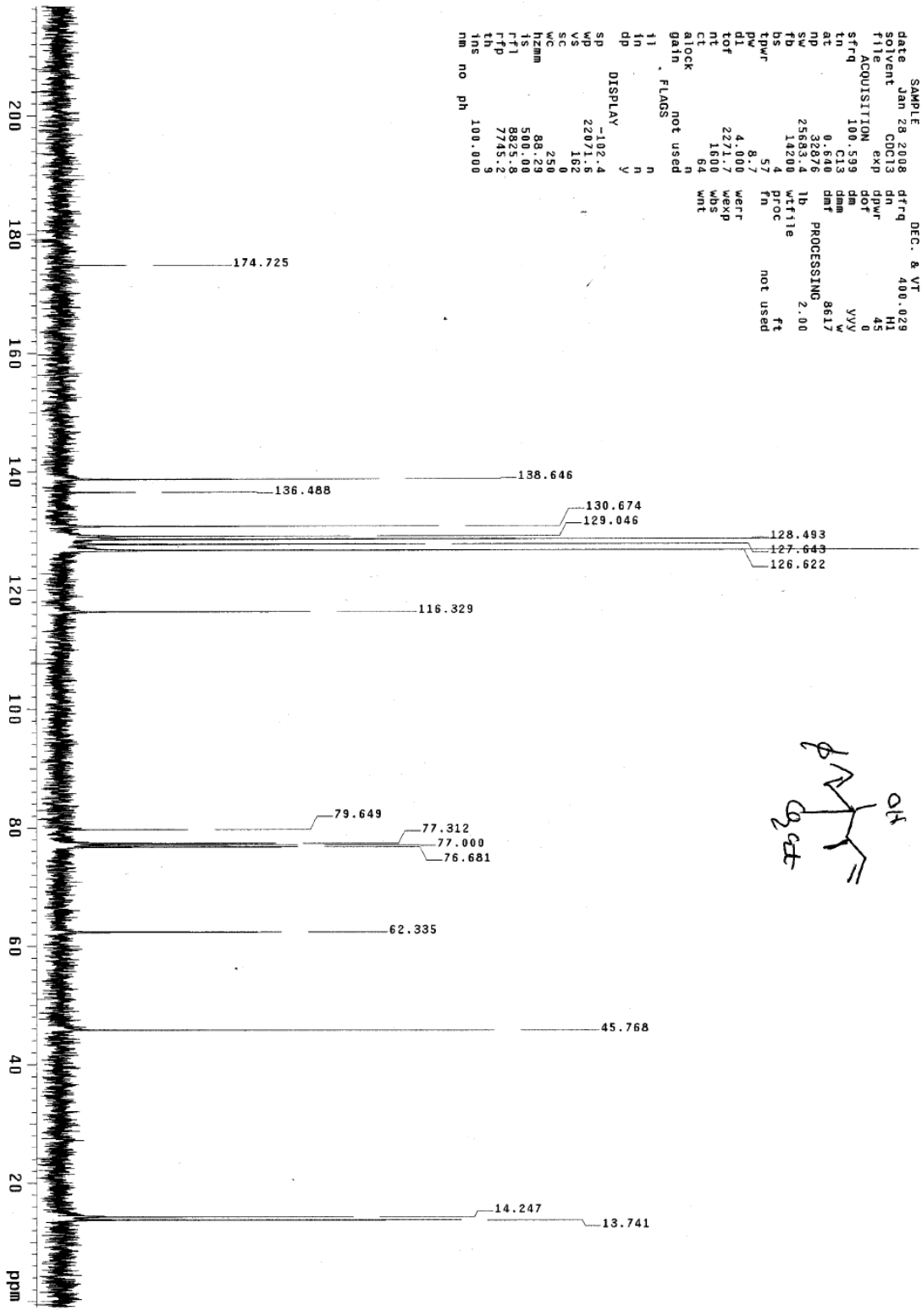
1.05
3.43
3.24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129.046
128.493
127.643
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77.312
77.000
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62.335
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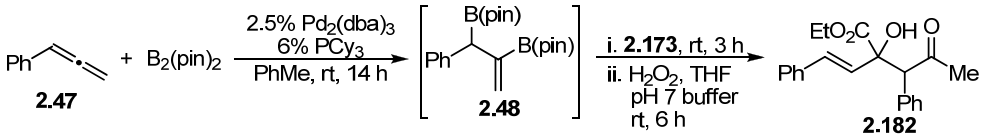
14.247
13.741
ppm

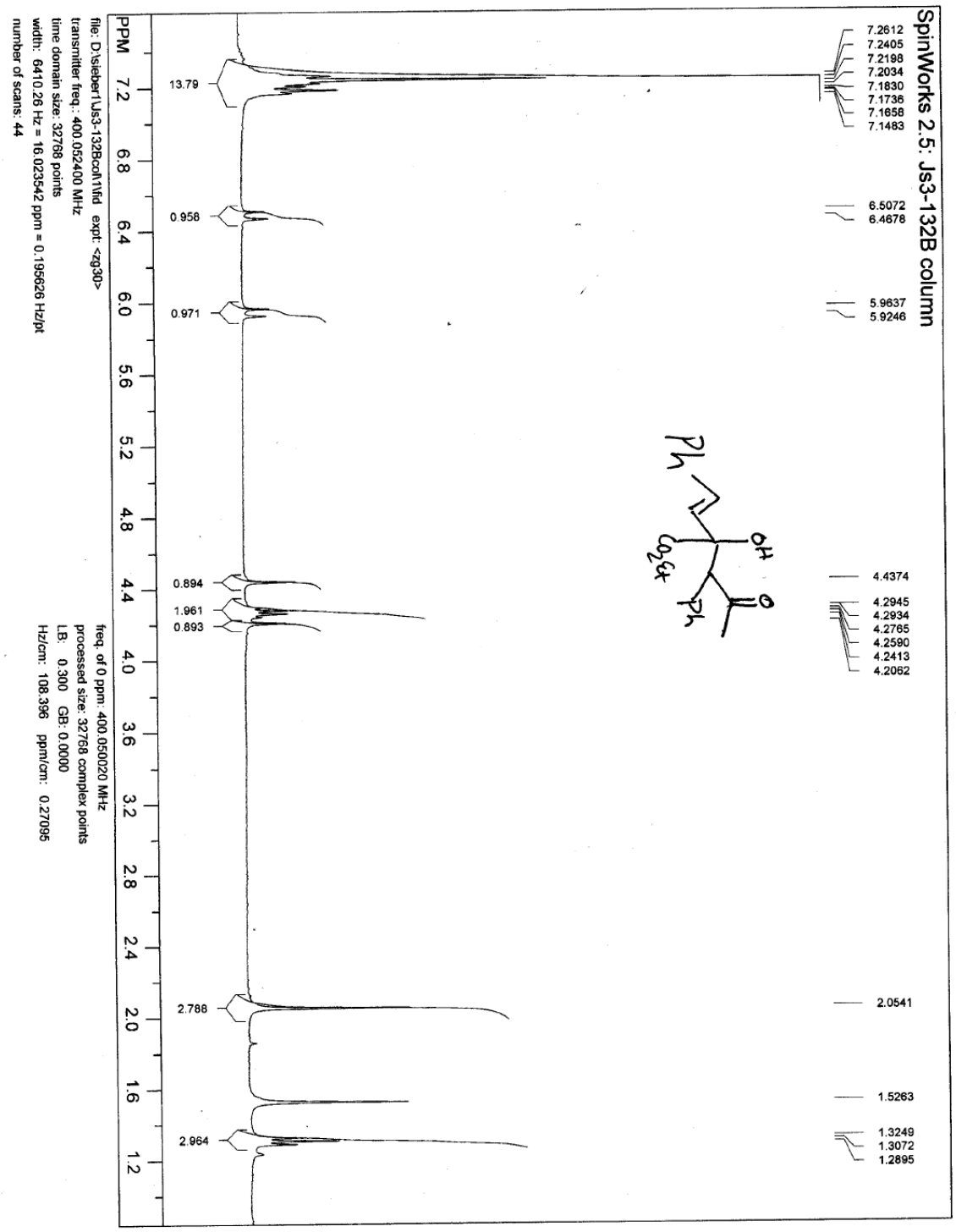
One-Pot Synthesis of 2.182



An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 6.0 mg (0.0065 mmol) of tris(dibenzylideneacetone)dipalladium(0), 4.4 mg (0.016 mmol) of tricyclohexylphosphine, and 0.52 mL of toluene in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 78.7 mg (0.310 mmol) of bis(pinacolato)diboron [$B_2(pin)_2$] was added followed by 30.0 mg (0.258 mmol) of phenyl allene (**2.47**). The vial was capped and allowed to stir at ambient temperature for 14 h. Next, 0.25 mL (0.17 mmol) of a 0.68 M stock solution of **2.173** in THF was added, and this mixture was allowed to stir for 3 h. After removal of volatile material under reduced pressure, 1.0 mL of THF, 0.76 mL of pH 7 buffer, and 0.30 mL of aqueous 30% H_2O_2 were added sequentially, and the resultant mixture was allowed to stir under N_2 for 6 h. The mixture was transferred to a separatory funnel and saturated aqueous $Na_2S_2O_3$ was added. This solution was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. Volatile material was removed under reduced pressure, and silica gel chromatography of the mixture afforded 41.2 mg (0.121 mmol, 71%) of **2.182** as a single diastereomer by ^1H NMR analysis. The relative stereochemistry was not determined.

(*E*)-Ethyl 2-hydroxy-4-oxo-3-phenyl-2-styrylpentanoate (2.182). A white solid. Mp = 110-120 ^oC. R_f = 0.31 (SiO_2, 4:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3510 (br, s),

3063 (m), 3025 (m), 2982 (m), 2924 (m), 2852 (m), 1881 (w), 1717 (s), 1607 (m), 1497 (m), 1455 (m), 1358 (s), 1231 (s), 1202 (s), 1134 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.10-7.40 (10H, m), 6.49 (1H, d, *J* = 16 Hz), 5.94 (1H, d, *J* = 16 Hz), 4.44 (1H, s), 4.27 (2H, q, *J* = 7.0 Hz), 4.21 (1H, s), 2.05 (3H, s), 1.31 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 209.2, 174.1, 136.3, 133.0, 131.5, 130.6, 128.42, 128.36, 127.9, 127.7, 127.5, 126.5, 78.40, 65.09, 62.26, 29.50, 14.17. LRMS (ESI+) Calcd for $C_{21}H_{22}O_4$ $(M - H_2O + H)^+$: 321.1, Found $(M - H_2O + H)^+$: 321.2.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5.9246
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4.2590
4.2413
4.2062
2.0541
1.5263
1.3249
1.3072
1.2895
13.79
0.958
0.971
0.894
1.961
0.893
2.788
2.964
PPM 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2
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transmitter freq.: 400.052400 MHz
time domain size: 32768 points
width: 6410.26 Hz = 16.023542 ppm = 0.195626 Hz/pt
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freq. of 0 ppm: 400.050020 MHz
processed size: 32768 complex points
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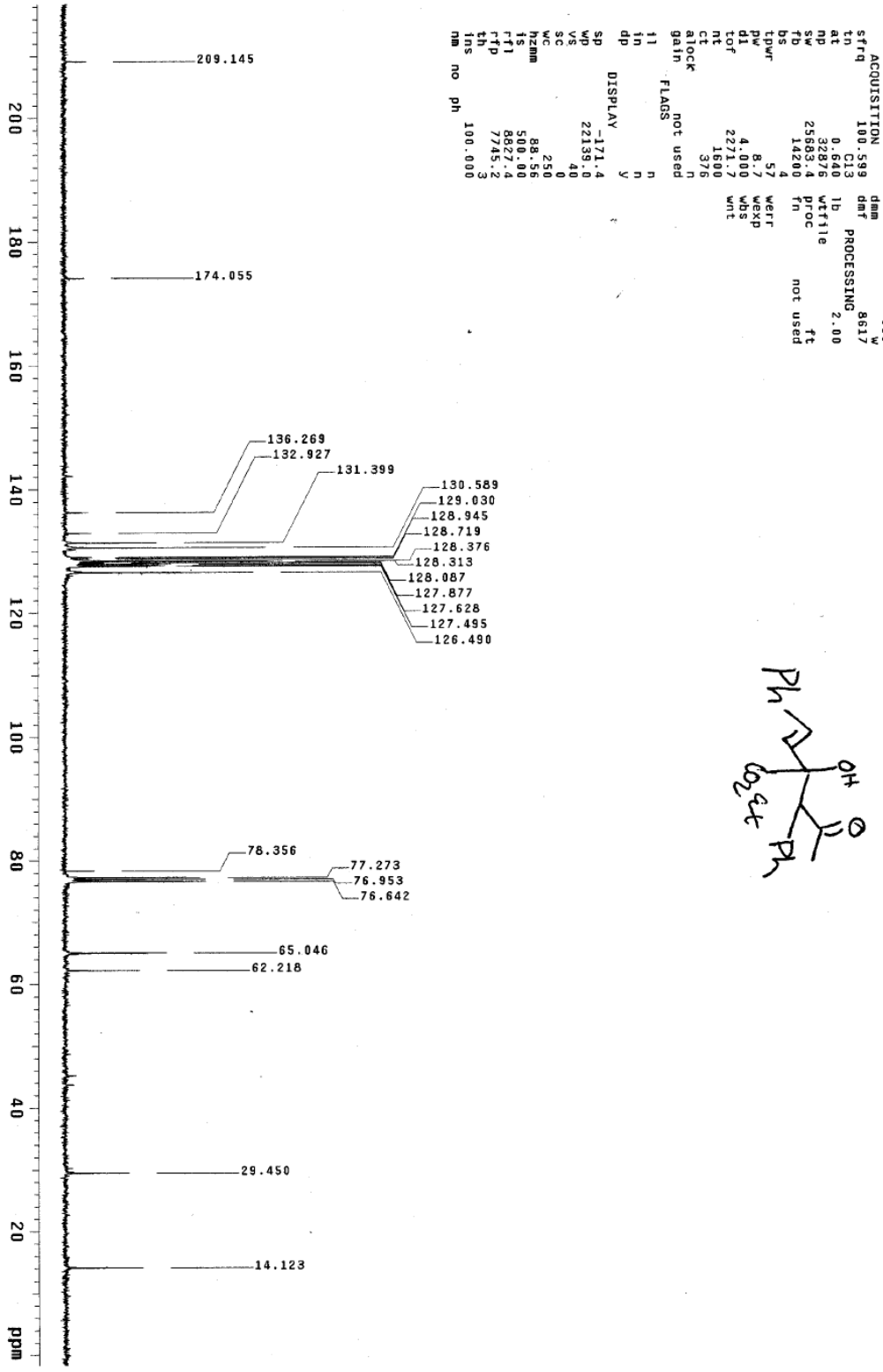
Hz/cm: 108.396 ppm/cm: 0.27095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126.490
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77.273
76.953
76.642
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62.218
29.450
14.123
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120
100
80
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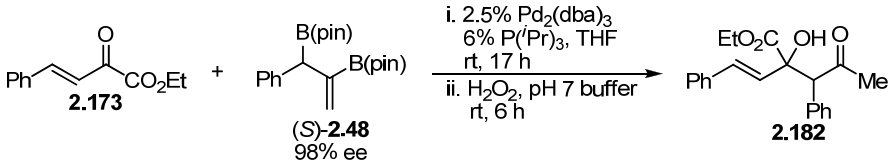
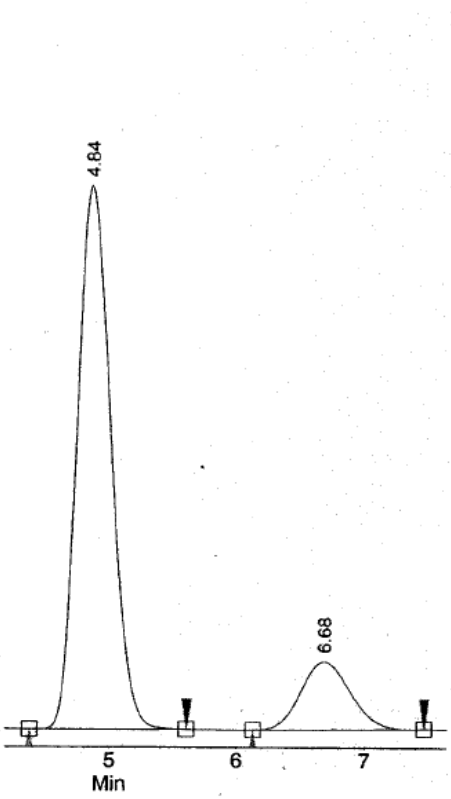
20
ppm
Ph
OH
O
CO2Et
Ph

Enantioselective Synthesis of 2.182

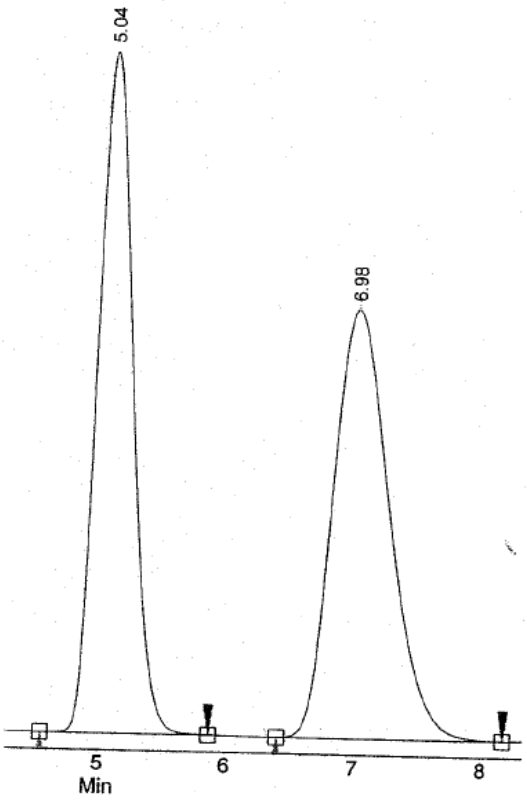


An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 1.6 mg (0.0018 mmol) of tris(dibenzylideneacetone)dipalladium(0) and 0.14 mL (0.0042 mmol) of a 0.030 M stock solution of triisopropylphosphine in THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 0.14 mL of THF, 0.15 mL (0.077 mmol) of a 0.50 M stock solution of (*S*)-**2.48** in THF, and 0.10 mL (0.070 mmol) of a 0.68 M stock solution of **2.173** in THF were added sequentially. The mixture was allowed to stir at ambient temperature for 17 h. After this time period, 0.30 mL of pH 7 buffer and 0.13 mL of aqueous 30% H_2O_2 were added, and the mixture allowed to stir for an additional 6 h. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the mixture using silica gel chromatography (hexanes/EtOAc) afforded 14.5 mg (0.0420 mmol, 60%) of **2.182** as a single diastereomer by ^{1}H NMR analysis. The enantiomeric purity of **2.182** was determined to be 70% ee using chiral SFC analysis. The absolute and relative stereochemistry of **2.182** was not determined.

*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 3.0 mL/min, 3.0 % MeOH) analysis of **2.182**:*

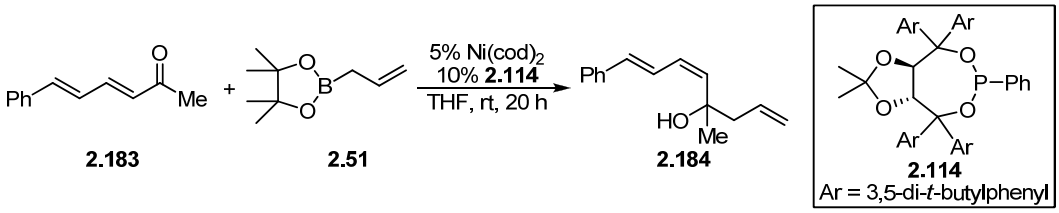


allylation-oxidation product



racemic

Synthesis of 2.184



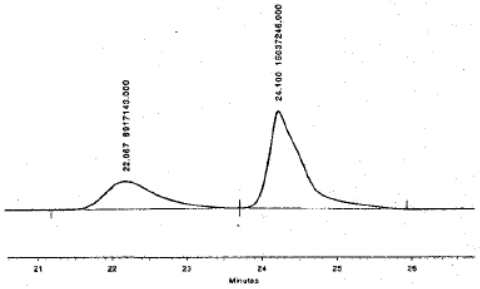
An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 2.0 mg (0.0073 mmol) of bis(1,5-cyclooctadiene)nickel(0), 14.8 mg (0.0145 mmol) of **2.114**, and 0.29 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 5 min. Next, 29.2 mg (0.174 mmol) of **2.51** and 25.0 mg (0.145 mmol) of **2.183**[1] were sequentially added. This mixture was allowed to stir at ambient temperature for 20 h, and then water was added, and the mixture was extracted with CH_2Cl_2. The combined organics were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. Purification using silica gel chromatography (hexanes/EtOAc) afforded 23.7 mg (0.111 mmol, 76%) of **2.184** as a white solid. The enantiomeric purity of **2.184** was determined to be 37% ee using chiral HPLC analysis. The absolute stereochemistry was not determined.

(5*Z*,7*E*)-4-Methyl-8-phenylocta-1,5,7-trien-4-ol (2.184). R_f = 0.15 (SiO_2, 15:1 hexanes:EtOAc); IR ($CDCl_3$ solution): 3430 (br, s), 3080 (s), 3000 (s), 2970 (s), 2928 (s), 1848 (w), 1708 (w), 1637 (m), 1599 (m), 1489 (s), 1447 (s), 1371 (s), 1341 (m), 1260 (m), 1151 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.70 (1H, dd, *J* = 16 Hz, *J* = 12 Hz), 7.42 (2H,

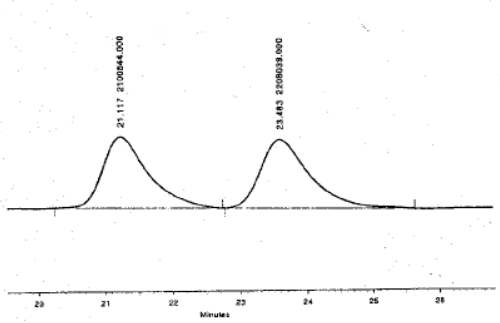
[1] **2.183** was prepared in 82% yield by Wittig reaction between (*E*)-cinnamaldehyde and 1-(triphenylphosphoranylidene)-2-proponane in refluxing toluene for 17 h.

d, *J* = 7.6 Hz), 7.30 (1H, t, *J* = 7.2 Hz), 7.21 (1H, t, *J* = 6.8 Hz), 6.48 (1H, d, *J* = 16 Hz), 6.14 (1H, t, *J* = 12 Hz), 5.80-5.95 (1H, m), 5.50 (1H, d, *J* = 12 Hz), 5.18 (1H, d, *J* = 10 Hz), 5.17 (1H, d, *J* = 17 Hz), 2.45 (1H, dd, *J* = 14 Hz, *J* = 6.8 Hz), 2.34 (1H, d, *J* = 14 Hz, *J* = 8.4 Hz), 1.88 (1H, s), 1.42 (3H, s); ^{13}C NMR ($CDCl_3$): δ 137.4, 136.6, 134.0, 133.6, 129.6, 128.5, 127.5, 126.6, 125.6, 119.3, 73.88, 48.50, 29.28. LRMS (ESI+) Calcd for $C_{15}H_{18}O$ $(M + H)^+$: 215.2, Found $(M + H)^+$: 215.2.

Chiral HPLC (Chiralcel-OD, Daicel, 0.7 % iPrOH in hexanes, 1.0 mL/min) analysis of ***2.184****:*



allylation product



racemic

js6-197column

expl std1h

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fb	3400	proc	ft
bs	4	fn	not used
tpwr	63		
pw	7.1	werr	
d1	4.000	wexp	
tof	0	wbs	
nt	8	wnt	
ct	8		
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gain	not used		
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il	n		
in	n		
dp	y		
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rfp	2896.2		
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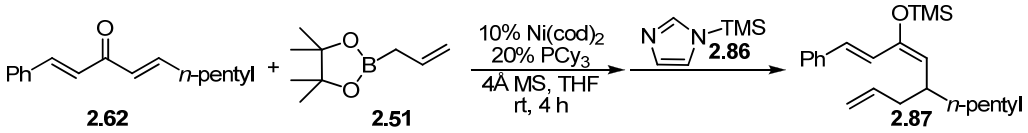
nm	ph		

5. Mechanistic Experiments

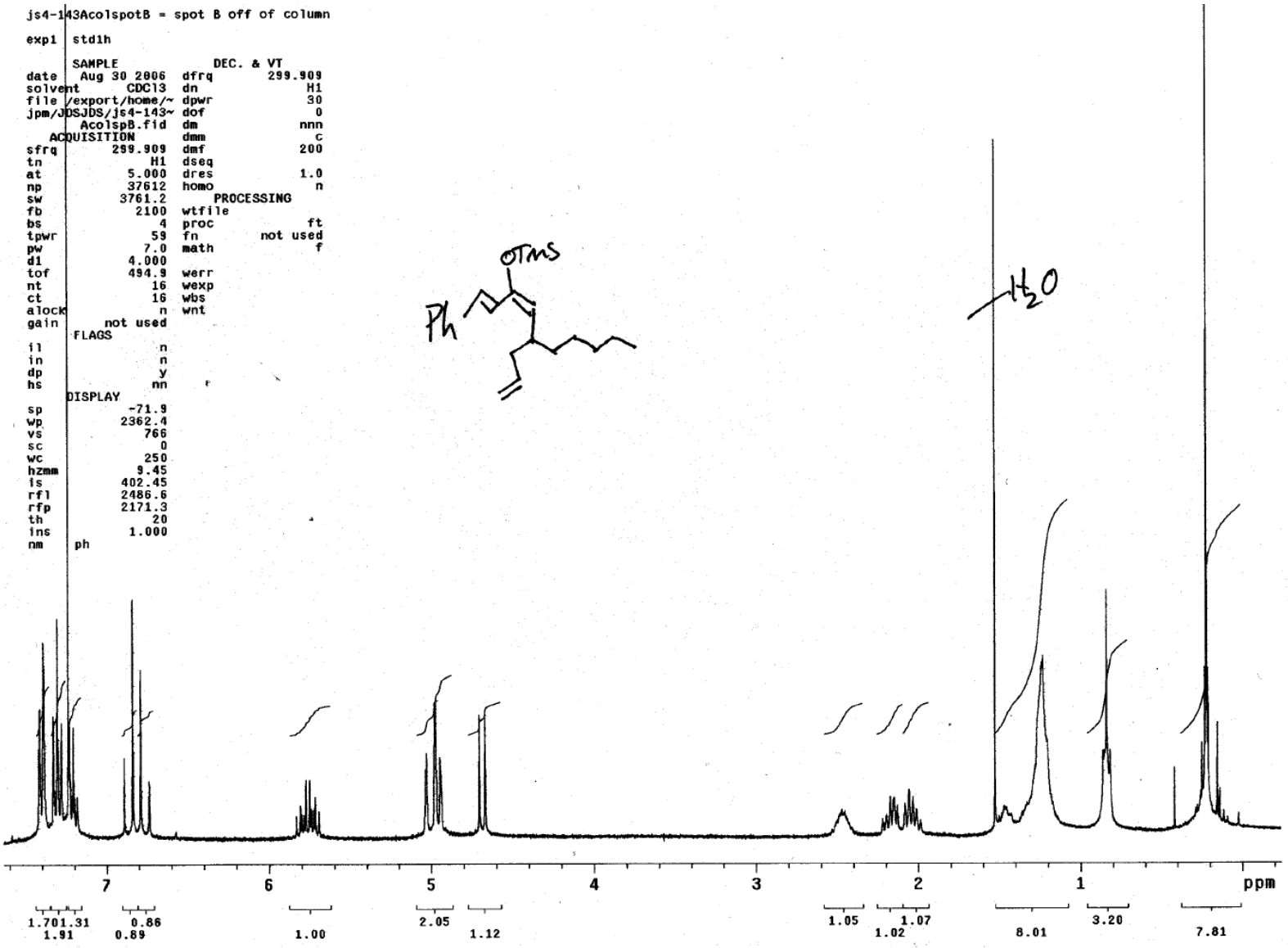
Synthesis of 2.87



An oven-dried 20 mL scintillation vial, equipped with a magnetic stir-bar, was charged with 5.9 mg (0.021 mmol) of bis(1,5-cyclooctadiene)nickel, 11.9 mg (0.0426 mmol) of tricyclohexylphosphine, 60 mg of activated, crushed 4Å molecular sieves, and 1.42 mL of THF in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 43.0 mg (0.256 mmol) of **2.51** was added followed by 48.6 mg (0.213 mmol) of **2.62**. The vial was capped, sealed with electrical tape, and allowed to stir at ambient temperature for 4 h. After this time period, 37.5 μL (0.256 mmol) of *N*-(trimethylsilyl)imidazole (**2.86**) was added and stirring was continued for an additional 1 h. Next, the mixture was filtered through a pad of celite using 10:1 hexanes:EtOAc, and volatile material was removed under reduced pressure. Purification of the mixture using silica gel chromatography (hexanes/EtOAc) afforded 52.3 mg (0.153 mmol, 72%) of **2.87**.

((1*E*,3*E*)-5-Allyl-1-phenyldeca-1,3-dien-3-yloxy)trimethylsilane (2.87). An oil. R_f = 0.12 (SiO_2, 150:1 hexanes:EtOAc); IR (neat): 3080 (m), 3063 (m), 3029 (m), 2962 (s), 2924 (s), 2852 (s), 1945 (w), 1810 (w), 1641 (m), 1607 (m), 1493 (m), 1447 (m), 1341 (m), 1248 (s), 1181 (m), 1147 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.42 (2H, d, *J* = 8.0 Hz), 7.32 (2H, t, *J* = 7.2 Hz), 7.12-7.25 (1H, m), 6.88 (1H, d, *J* = 16 Hz), 6.78 (1H, d, *J* = 16

Hz), 5.78 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 6.8 Hz), 4.92-5.08 (2H, m), 4.70 (1H, d, *J* = 10 Hz), 2.35-2.60 (1H, m), 2.11-2.24 (1H, m), 1.99-2.11 (1H, m), 1.41-1.56 (1H, m), 1.15-1.41 (7H, m), 0.86 (3H, t, *J* = 6.8 Hz), 0.24 (9H, s); ^{13}C NMR ($CDCl_3$): δ 147.7, 137.4, 137.0, 128.9, 128.5, 127.4, 126.7, 121.9, 119.4, 115.8, 41.01, 37.17, 35.96, 32.04, 27.07, 22.67, 14.12, 0.36. LRMS (ESI+) Calcd for $C_{22}H_{34}OSi$ $(M + H)^+$: 343.3, Found $(M + H)^+$: 343.2.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AcolspB.fid
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dmm c
dmf 200
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PROCESSING
wtfile
proc ft
fn not used
math f
werr
wexp
wbs
wnt
OTMS
Ph
H2O
7
6
5
4
3
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1
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1.31
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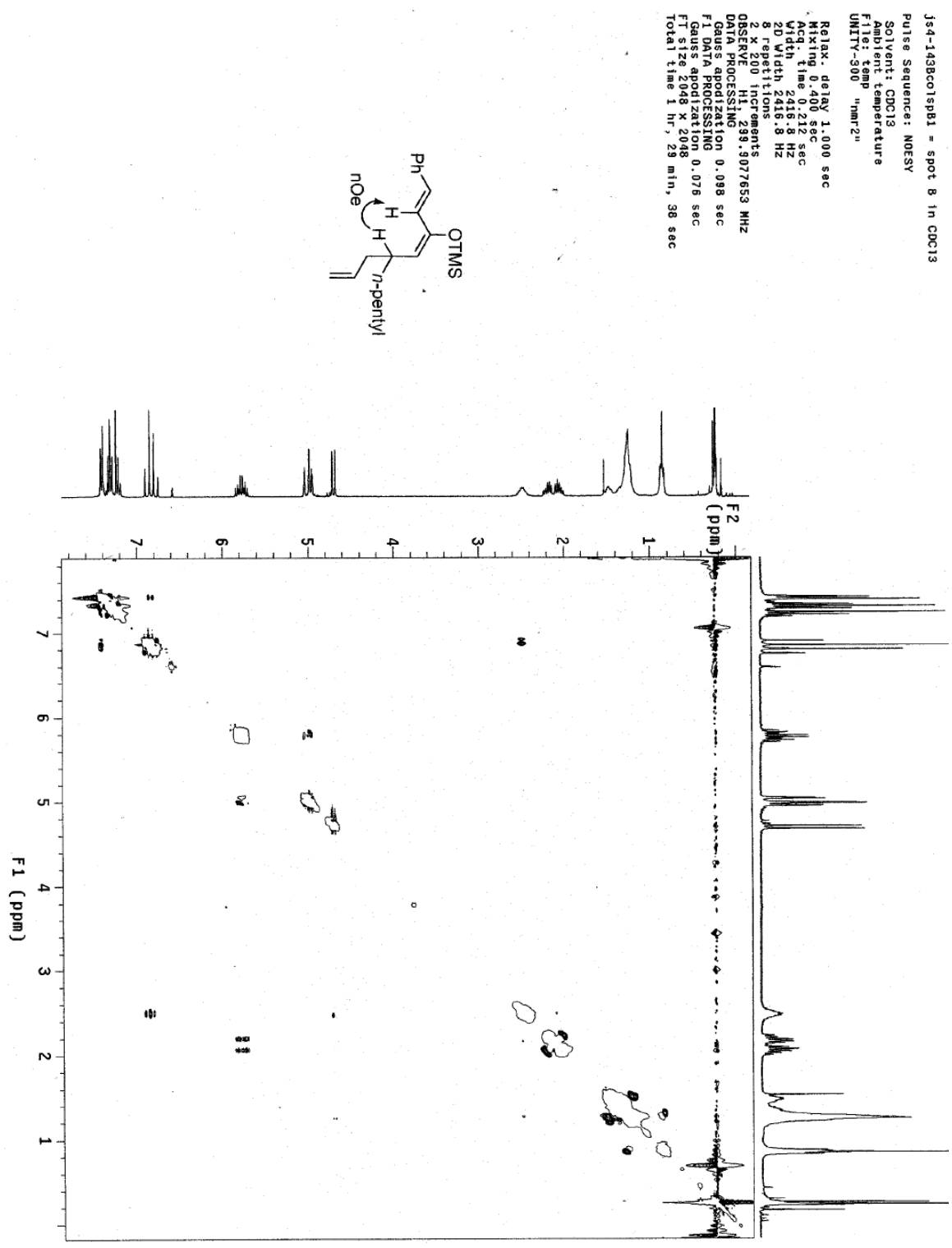
8.01
3.20
7.81

NOESY of **2.87**: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2D Width 2416.8 Hz
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Gauss apodization 0.076 sec
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H
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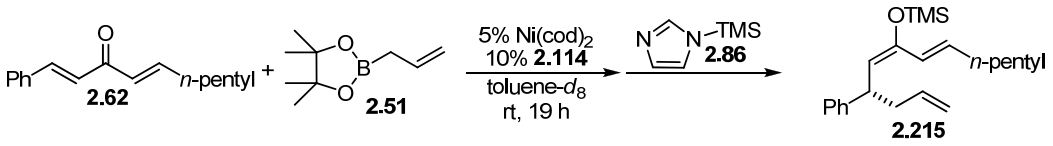
F2 (ppm)
F1 (ppm)

Synthesis of 2.215

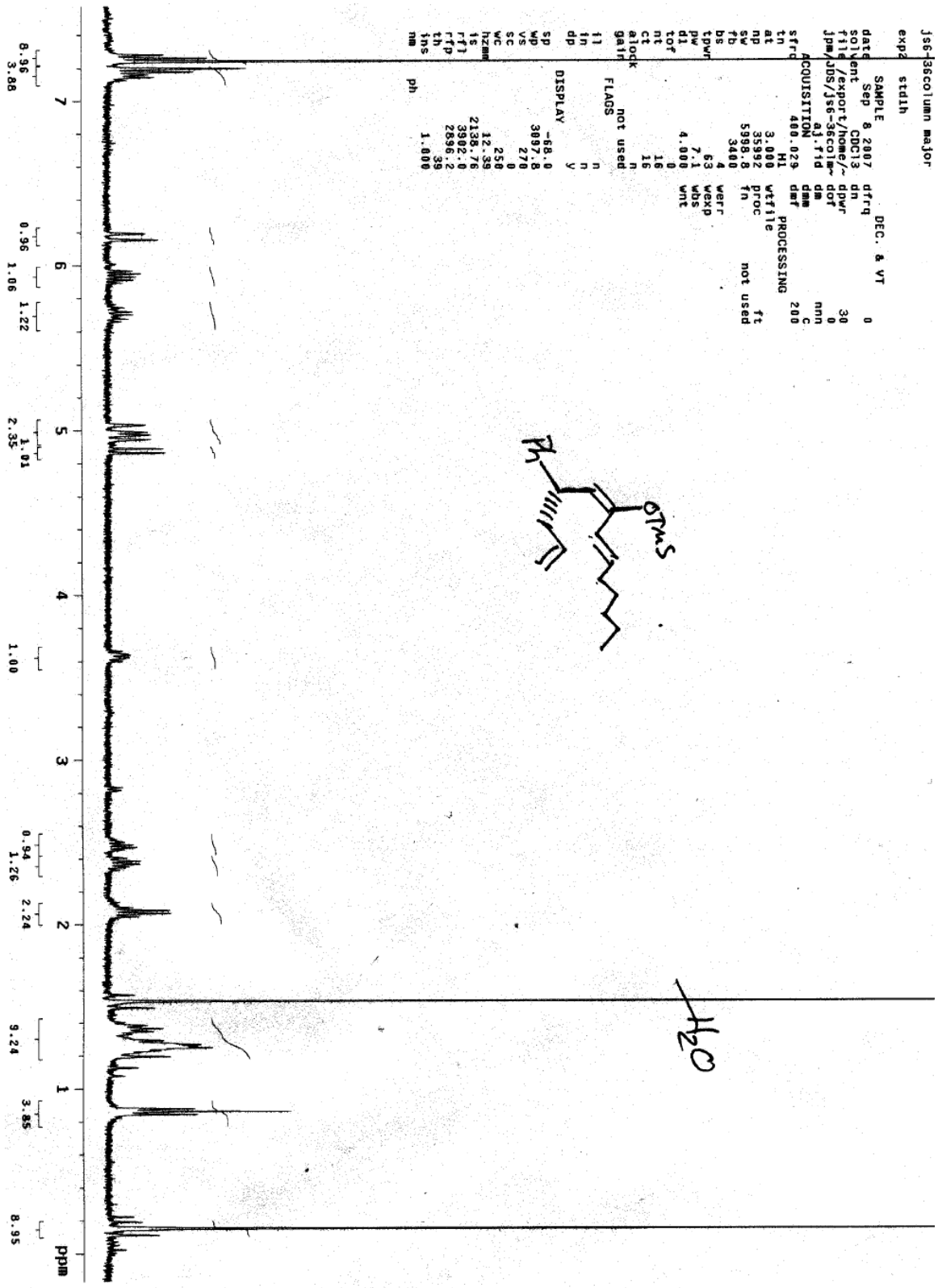


An oven-dried 2-dram vial equipped with a magnetic stir-bar was charged with 2.3 mg (0.0084 mmol) of bis(1,5-cyclooctadiene)nickel, 17.2 mg (0.0168 mmol) of **2.114**, and 0.84 mL of toluene-d_8 in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 42.3 mg (0.252 mmol) of **2.51** was added followed by 38.4 mg (0.168 mmol) of **2.62**. The vial was capped, sealed with electrical tape, and allowed to stir at ambient temperature for 19 h. After this time period, 36.9 μL (0.252 mmol) of *N*-(trimethylsilyl)imidazole (**2.86**) was added and stirring was continued for an additional 1 h. Next, the mixture was filtered through a pad of celite using 10:1 hexanes:EtOAc, and volatile material was then removed under reduced pressure. Purification of the mixture using silica gel chromatography (hexanes/EtOAc) afforded 29.8 mg (0.0870 mmol, 52%) of **2.215**. In addition, 8.2 mg (0.024 mmol) of a 1:4.5 mixture of **2.87**:(*Z*)-**2.215** was isolated (66% combined yield). Following the reaction by ^{1}H NMR verified that (*E*)-**2.215** was initially formed, and that as the reaction progressed, (*E*)-**2.215** slowly isomerized to (*Z*)-**2.215**.[1]

Trimethyl[(*S*,5*E*,7*E*)-4-phenyltrideca-1,5,7-trien-6-yloxy]silane (2.215). An oil. R_f = 0.17 (SiO_2, 70:1 hexanes:EtOAc); IR (neat): 3067 (m), 3029 (m), 2958 (s), 2920 (s), 2860 (s), 1658 (m), 1599 (m), 1497 (m), 1455 (m), 1366 (m), 1244 (s), 1189 (m), 1130

[1] Note that the *E* and *Z* descriptors used here represent the geometry of the silyl enol ether.

(m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.21-7.30 (2H, m), 7.10-7.21 (3H, m), 6.35 (1H, d, *J* = 15 Hz), 5.93 (1H, dt, *J* = 15 Hz, *J* = 6.8 Hz), 5.64-5.78 (1H, m), 5.01 (1H, d, *J* = 18 Hz), 4.96 (1H, d, *J* = 10 Hz), 4.88 (1H, d, *J* = 10 Hz), 3.58-3.68 (1H, m), 2.44-2.54 (1H, m), 2.30-2.42 (1H, m), 2.08 (2H, q, *J* = 7.2 Hz), 1.18-1.42 (6H, m), 0.86 (3H, t, *J* = 6.4 Hz), 0.15 (9H, s); ^{13}C NMR ($CDCl_3$): δ 147.5, 145.3, 136.6, 132.8, 128.3, 127.2, 125.9, 122.8, 116.1, 114.3, 42.47, 41.93, 32.57, 31.52, 28.95, 22.55, 14.08, 0.035. LRMS (ESI+) Calcd for $C_{22}H_{34}OSi$ $(M + H)^+$: 343.3, Found $(M + H)^+$: 343.3.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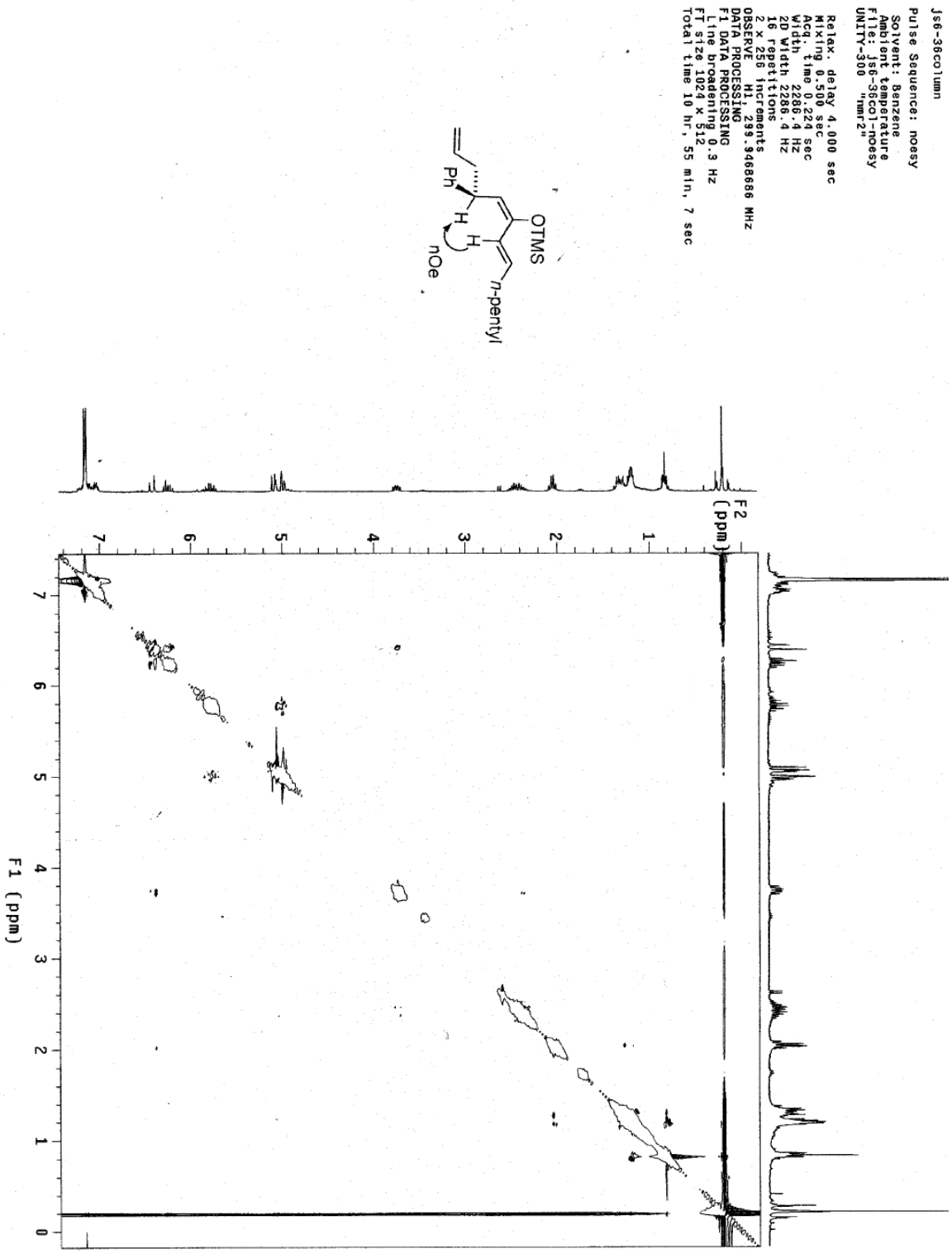
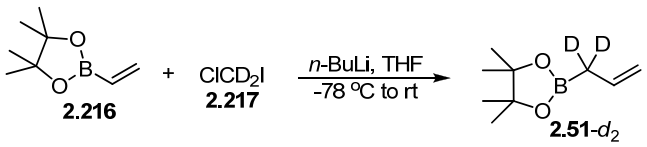
NOESY of **2.215**:



Deuterium labeling experiments:

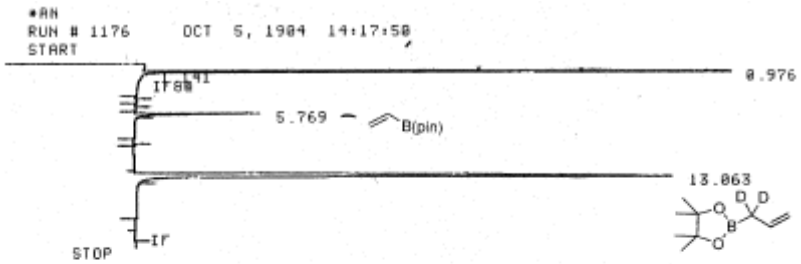
Synthesis of Allylboronic Acid Pinacol Ester-d_2 (2.51-d_2)[1]



To 0.665 g (4.32 mmol) of vinylboronic acid pinacol ester (**2.216**) and 1.00 g (5.61 mmol) of chloroiodomethane-d_2 (**2.217**)[2] in 17 mL of THF at –78 °C was added 2.07 mL (5.2 mmol) of 2.5 M *n*-BuLi in hexane dropwise over 15 min. The reaction was then allowed to warm to room temperature and allowed to stir overnight. The reaction was then concentrated under reduced pressure. The residue was diluted with pentane and filtered through celite. Saturated aqueous NH_4Cl was added, and the two layers were filtered through celite. The organic layer was collected, and the aqueous layer extracted with pentane. The organic material was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the mixture using silica gel chromatography (pentane/CH_2Cl_2) gave 0.249 g (1.46 mmol, 34%) of **2.51**-d_2 as a colorless oil that was contaminated with 8% of **2.216** as determined by GLC analysis.

[1] For lead reference, see: Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687.
[2] Purchased from Cambridge Isotopes or prepared from CD_2Cl_2 according to: Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2864.

Achiral GLC (Ultra 1, Hewlett-Packard, 35 °C) analysis of isolated ***2.51***-d_2*:*

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DIRECTORY FULL
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   5.769      47796   PB    .128     .38800
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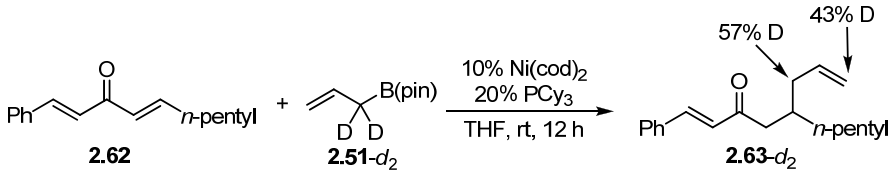
Non-Enantioselective Conjugate Allylation with 2.51-d_2 and Ni(cod)$_2$

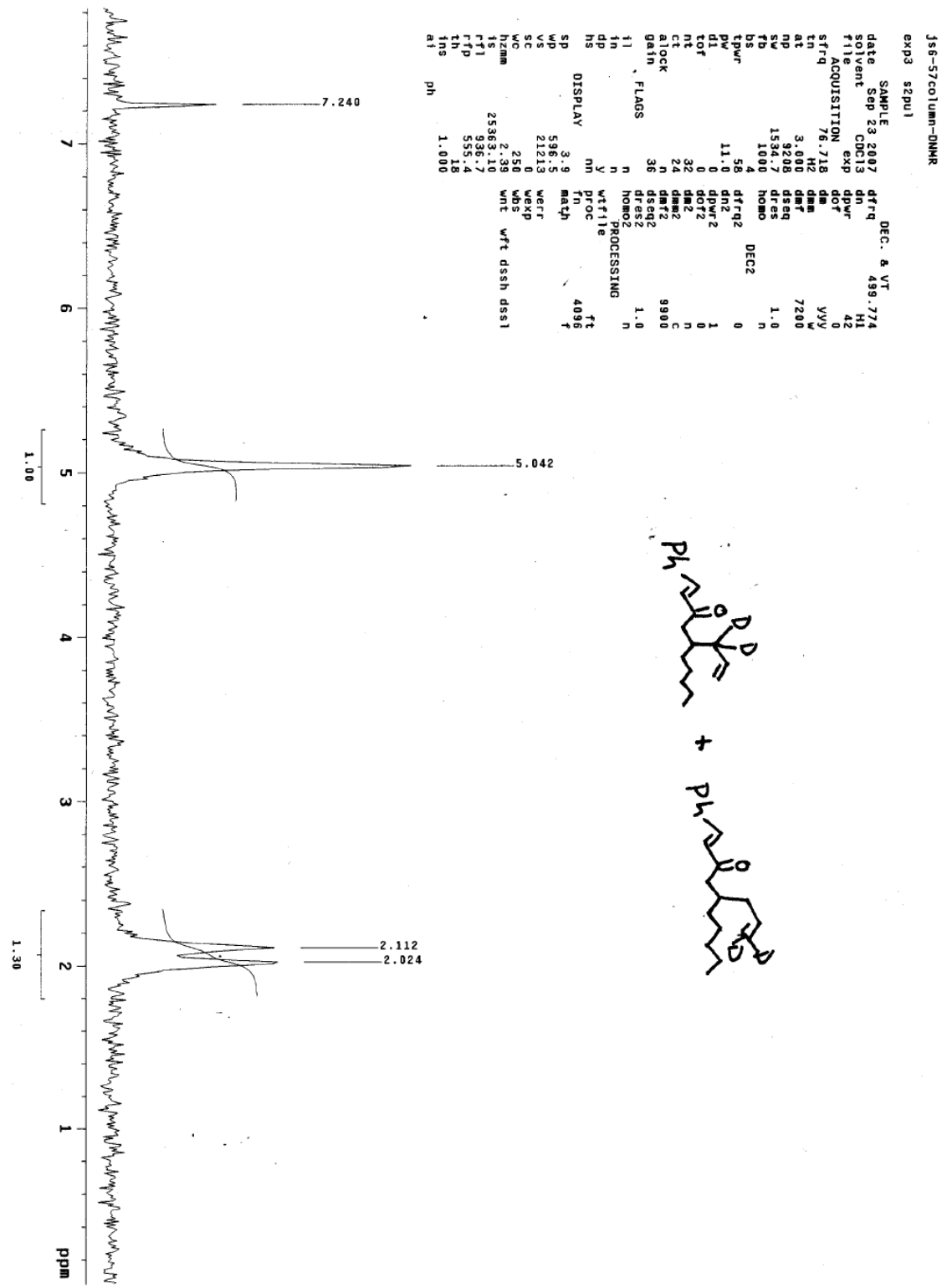


2.62 **2.51**-d_2 **2.63**-d_2

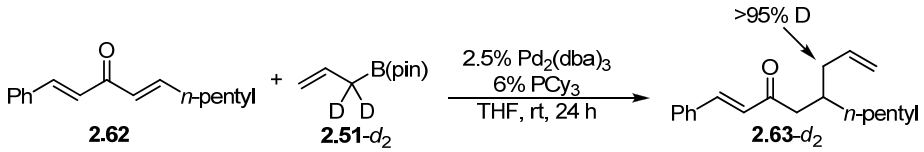
An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 3.0 mg (0.011 mmol) of bis(1,5-cyclooctadiene)nickel, 6.1 mg (0.022 mmol) of PCy_3, and 0.73 mL of THF-d_8 in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 53.7 μL (0.131 mmol) of a 2.44 M stock solution of **2.51**-d_2 in toluene-d_8 was added, followed by 25.0 mg (0.109 mmol) of **2.62**. The vial was capped, sealed with electrical tape, removed from the dry-box, and allowed to stir at

ambient temperature for 12 h. After this time period, degassed water (N_2 sparge) was added, and the mixture transferred to a separatory funnel with CH_2Cl_2. After swirling the layers, the organic layer was collected, and the aqueous layer washed with CH_2Cl_2 (2x). The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. Analysis of the unpurified reaction mixture using achiral GLC was used to determine the chemoselectivity of the reaction. ^{1}H NMR analysis of the unpurified material verified that the label in unreacted **2.51**-d_2 had not been scrambled. Silica gel chromatography of the mixture (hexanes/EtOAc) afforded 16.8 mg (0.0617 mmol, 57%) of **2.63**-d_2. The deuterium label ratios were determined by ^{2}H NMR analysis of the purified material.

^{2}H NMR spectrum of conjugate allylation product **2.63**-d_2 using Ni/PCy_3 as catalyst:

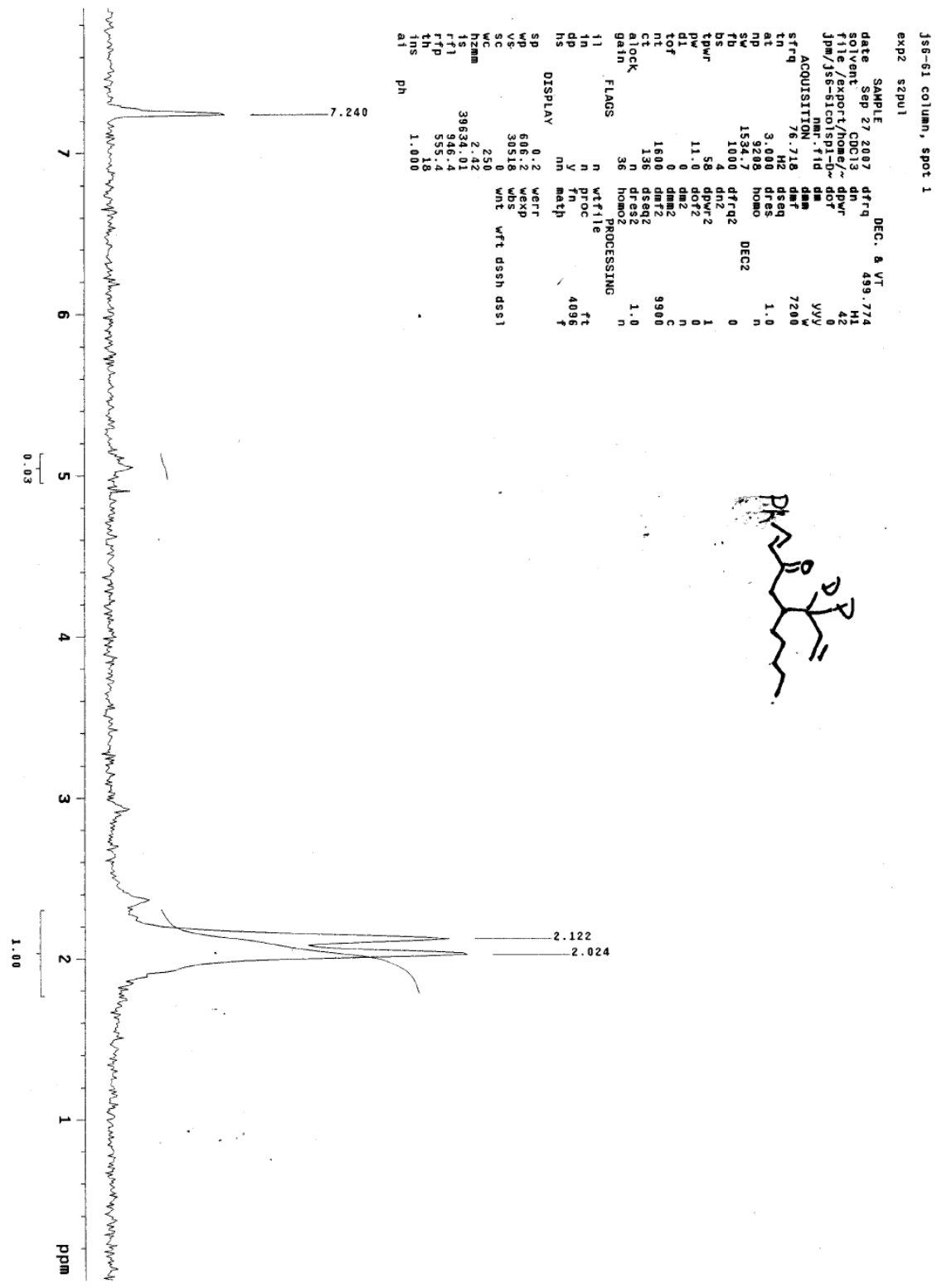


Non-Enantioselective Conjugate Allylation with 2.51-d_2 and $Pd_2(dba)_3$

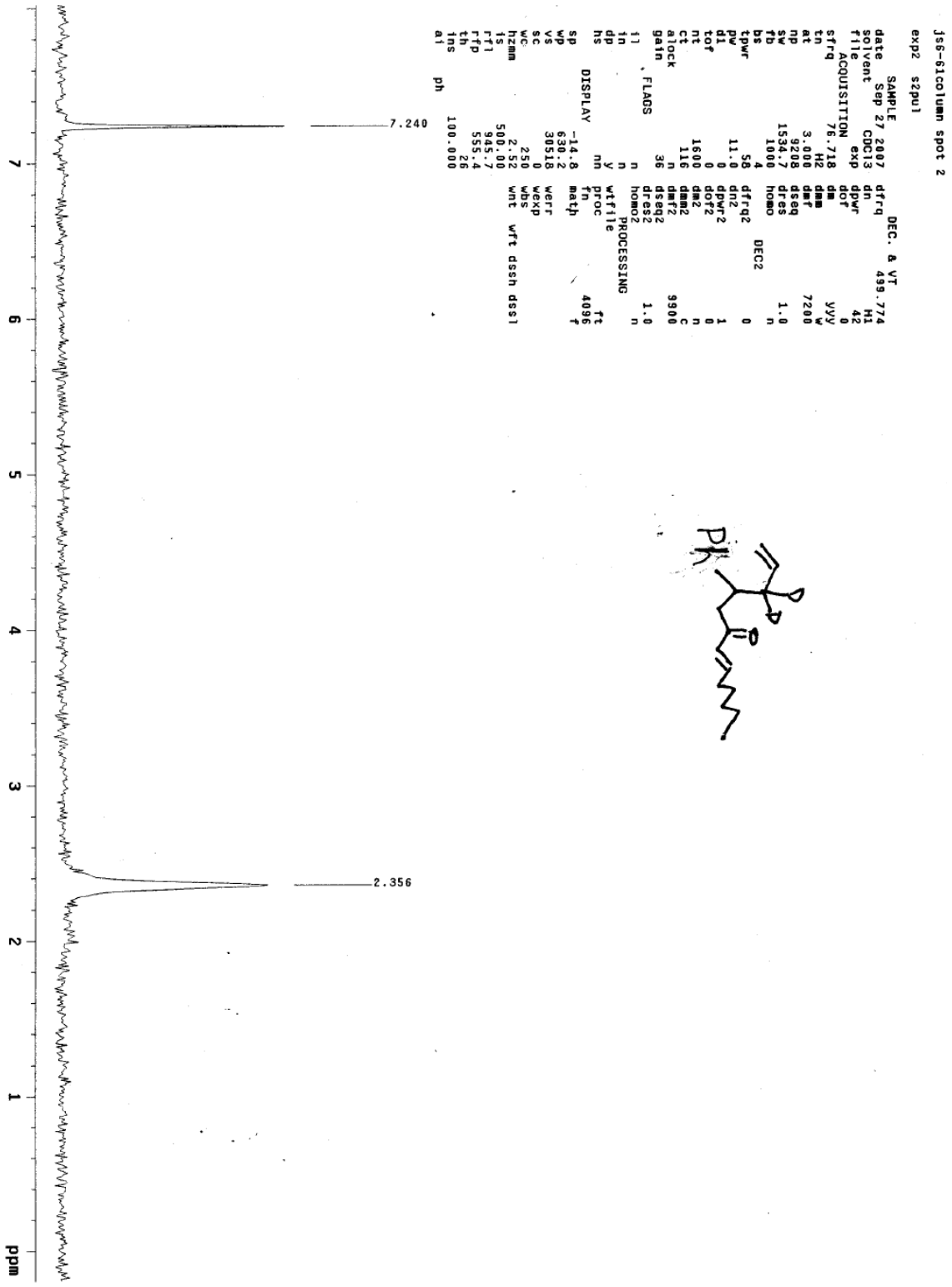


An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 2.5 mg (0.0027 mmol) of bis(dibenzylideneacetone)dipalladium, 1.8 mg (0.0065 mmol) of PCy_3, and 0.72 mL of THF-d_8 in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 62.7 μL (0.153 mmol) of a 2.44 M stock solution of **2.51**-d_2 in toluene-d_8 was added, followed by 25.0 mg (0.109 mmol) of **2.62**. The vial was capped, sealed with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 24 h. After this time period, degassed water (N_2 sparge) was added, and the mixture transferred to a separatory funnel with CH_2Cl_2. After swirling the layers, the organic layer was collected, and the aqueous layer washed with CH_2Cl_2 (2x). The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. Analysis of the unpurified reaction mixture using achiral GLC was used to determine the chemoselectivity of the reaction. ^{1}H NMR analysis of the unpurified mixture verified that the label in unreacted **2.51**-d_2 had not been scrambled. Silica gel chromatography of the mixture (hexanes/EtOAc) afforded 9.3 mg (0.034 mmol, 31%) of **2.63**-d_2. The deuterium label ratios were determined by ^{2}H NMR analysis of the purified material.

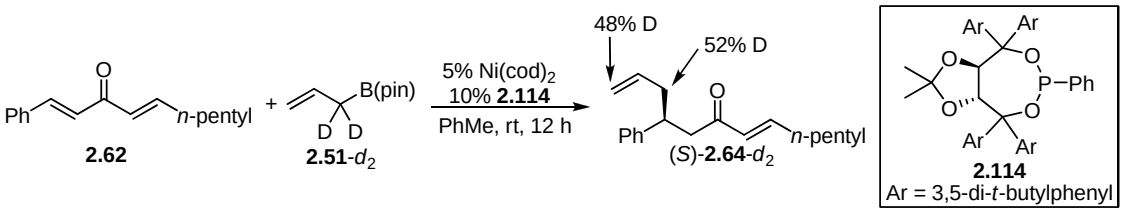
^{2}H NMR spectrum of conjugate allylation product using Pd/PCy_3 as catalyst:



^{2}H NMR spectrum of conjugate allylation product using Pd/PCy_3 as catalyst:

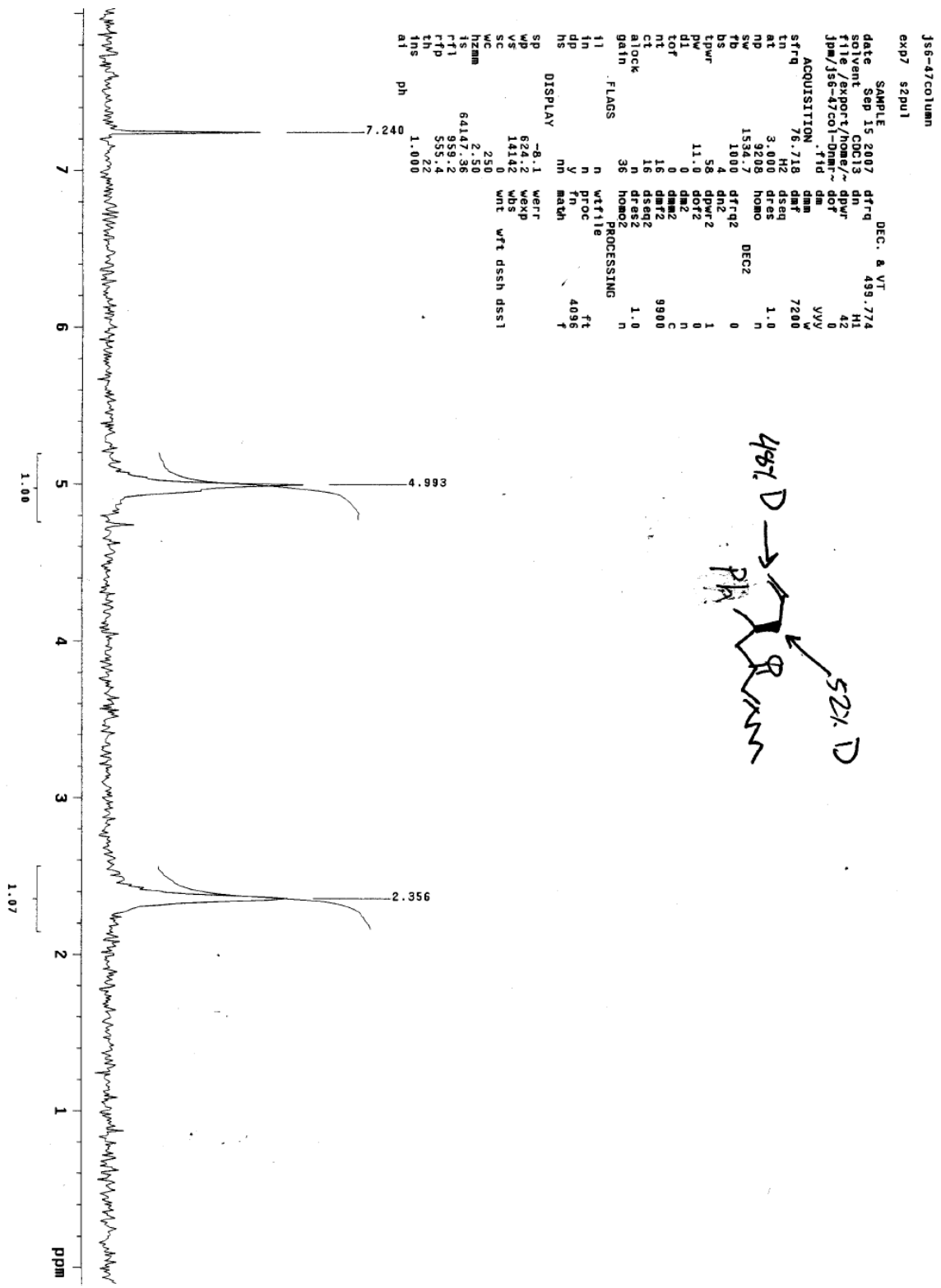


Enantioselective Conjugate Allylation with 2.51-d_2

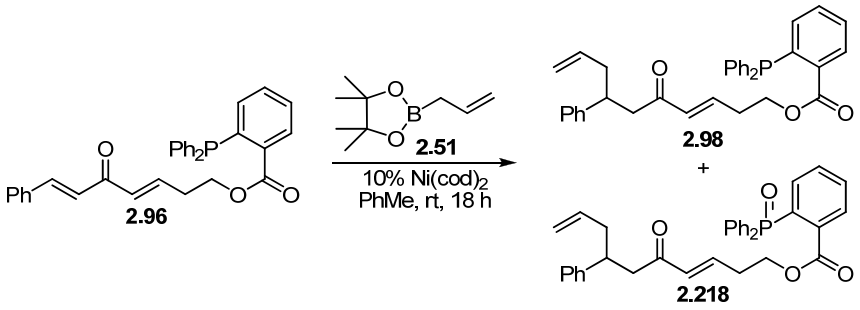


An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 2.2 mg (0.0082 mmol) of bis(1,5-cyclooctadiene)nickel, 16.7 mg (0.0163 mmol) of **2.114**, and 0.23 mL of toluene-d_8 in a dry-box under an argon atmosphere. The vial was capped and allowed to stir for 45 min. Next, 100.0 μL (0.244 mmol) of a 2.44 M stock solution of **2.51**-d_2 in toluene-d_8 was added, followed by 37.2 mg (0.163 mmol) of **2.62**. The vial was capped, taped with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 12 h. After this time period, degassed water (N_2 sparge) was added, and the mixture transferred to a separatory funnel with CH_2Cl_2. After swirling the layers, the organic layer was collected, and the aqueous layer washed with CH_2Cl_2 (2x). The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. Analysis of the unpurified reaction mixture using achiral GLC was used to determine the chemoselectivity of the reaction. ^{1}H NMR analysis of the unpurified mixture verified that the label in unreacted **2.51**-d_2 had not been scrambled. Silica gel chromatography of the mixture (hexanes/EtOAc) afforded 9.1 mg (0.033 mmol, 20%) of (*S*)-**2.64**-d_2. The deuterium label ratios were determined by ^{2}H NMR analysis of the purified material.

^{2}H NMR spectrum of conjugate allylation product using Ni/**2.114** as catalyst:



Synthesis of 2.98



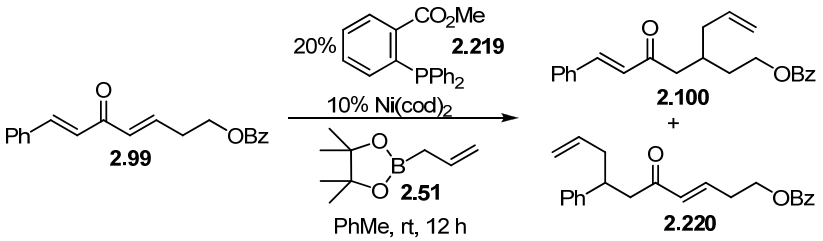
A 2-dram vial with magnetic stir-bar was charged with 2.2 mg (0.0082 mmol) of bis(1,5-cyclooctadiene)nickel and 40.0 mg (0.0815 mmol) of **2.96** in a dry-box under an argon atmosphere. Toluene (0.41 mL) was then added followed by 16.4 mg (0.0978 mmol) of allylboronic acid pinacol ester (**2.51**). The vial was capped, sealed with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 18 h. The reaction was quenched with the addition of 2 drops (18 gauge needle) of MeOH and subsequently, concentrated under reduced pressure. Chemoselectivity was determined by ^{1}H NMR analysis of the unpurified mixture. Purification by flash chromatography (SiO_2, hexanes/EtOAc) afforded 17.1 mg (0.0321 mmol) of **2.98** along with 9.3 mg (0.017 mmol) of oxidized material (**2.218**) (combined yield = 60%).

(*E*)-5-Oxo-7-phenyldeca-3,9-dienyl 2-(diphenylphosphino)benzoate (2.98). R_f = 0.17 (SiO_2, 6:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3400 (br w), 3067 (m), 2919 (m), 28528 (m), 1953 (w), 1716 (s), 1670 (s), 1632 (m), 1429 (s), 1265 (s), 1243 (s), 1138 (s), 1113 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.95-8.02 (1H, m), 7.31-7.41 (2H, m), 7.26-7.31 (6H, m), 7.19-7.26 (6H, m), 7.10-7.18 (3H, m), 6.88-6.94 (1H, m), 6.63 (1H, dt, *J* = 16 Hz, *J* =

6.8 Hz), 6.01 (1H, d, *J* = 16 Hz), 5.61 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 6.8 Hz), 4.88-4.99 (2H, m), 4.20 (2H, t, *J* = 6.4 Hz), 3.27 (1H, p, *J* = 7.2 Hz), 2.82 (2H, app d, J = 7.6 Hz), 2.40 (2H, q, *J* = 6.8 Hz), 2.36 (2H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 198.6, 166.6, 144.1, 142.1, 140.4, 140.1, 137.8, 137.7, 136.1, 134.3, 133.9, 133.7, 132.3, 132.0, 130.6, 128.6, 128.5, 128.4, 128.3, 128.2, 127.5, 126.3, 63.03, 46.20, 40.96, 40.63, 31.53. ^{31}P NMR ($CDCl_3$): δ -3.10. LRMS (ESI+) Calcd for $C_{35}H_{33}O_3P$ $(M + H)^+$: 533.2, Found $(M + H)^+$: 533.1.

(*E*)-5-Oxo-7-phenyldeca-3,9-dienyl 2-(diphenylphosphoryl)benzoate (2.218). R_f = 0.17 (SiO_2, 1:3 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3422 (br m), 3058 (m), 2928 (m), 2856 (m), 1966 (w), 1733 (s), 1661 (s), 1628 (m), 1433 (s), 1281 (s), 1256 (s), 1197 (s), 1121 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.80-7.88 (1H, m), 7.52-7.68 (5H, m), 7.30-7.52 (8H, m), 7.10-7.29 (5H, m), 6.51 (1H, dt, *J* = 16 Hz, *J* = 6.8 Hz), 5.89 (1H, d, *J* = 16 Hz), 5.61 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 7.2 Hz), 4.88-4.98 (2H, m), 4.00 (2H, t, *J* = 6.8 Hz), 3.26 (1H, p, *J* = 7.2 Hz), 2.74-2.86 (2H, m), 2.35 (2H, t, *J* = 7.2 Hz), 2.20 (2H, q, *J* = 6.8 Hz); ^{31}P NMR ($CDCl_3$): δ 32.72. LRMS (ESI+) Calcd for $C_{35}H_{33}O_4P$ $(M + H)^+$: 549.2, Found $(M + H)^+$: 549.1.

Synthesis of 2.100



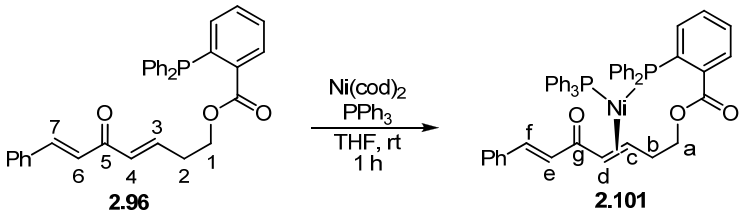
An oven-dried vial with stir-bar was charged with 2.0 mg (0.0074 mmol) of bis(1,5-cyclooctadiene)nickel, 4.7 mg (0.015 mmol) of ligand **2.219**, and 0.98 mL of toluene in a dry-box under an argon atmosphere. To this solution was added 29.6 mg (0.176 mmol) of **2.51** and 45.0 mg (0.147 mmol) of **2.99**. The vial was sealed, removed from the dry-box, and allowed to stir at ambient temperature for 12 h. After this time period, degassed water (N_2 sparge) was added, and the mixture transferred to a separatory funnel with CH_2Cl_2. The organic layer was collected, and the aqueous layer washed with CH_2Cl_2 (2x). The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. Chemoselectivity was determined by ^{1}H NMR analysis of the unpurified mixture. Purification of the mixture using silica gel chromatography (hexanes/EtOAc) afforded 38.4 mg (0.110 mmol, 75%) of the conjugate allylation products **2.100** and **2.220**.

(*E*)-3-Allyl-5-oxo-7-phenylhept-6-enyl benzoate (2.100). An oil. R_f = 0.23 (SiO_2, 6:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3067 (m), 2915 (m), 2852 (m), 1961 (w), 1716 (s), 1666 (s), 1610 (s), 1450 (m), 1272 (s), 1117 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.01 (2H, d, *J* = 8 Hz), 7.28-7.61 (9H, m), 6.72 (1H, d, *J* = 16 Hz), 5.79 (1H, ddt, *J* = 17 Hz, *J* = 10

Hz, *J* = 7.2 Hz), 5.00-5.12 (2H, m), 4.30-4.45 (2H, m), 2.71 (1H, dd, *J* = 16 Hz, *J* = 6.8 Hz), 2.66 (1H, dd, *J* = 16 Hz, *J* = 6.8 Hz), 2.37 (1H, h, *J* = 6.4 Hz), 2.09-2.29 (2H, m), 1.72-1.92 (2H, m); ^{13}C NMR ($CDCl_3$): δ 199.3, 166.5, 142.5, 135.8, 134.4, 132.8, 130.4, 130.2, 129.5, 128.8, 128.3, 128.2, 126.3, 117.3, 63.00, 44.88, 38.26, 32.58, 31.23. LRMS (ESI+) Calcd for $C_{23}H_{24}O_3$ $(M + H)^+$: 349.2, Found $(M + H)^+$: 349.1.

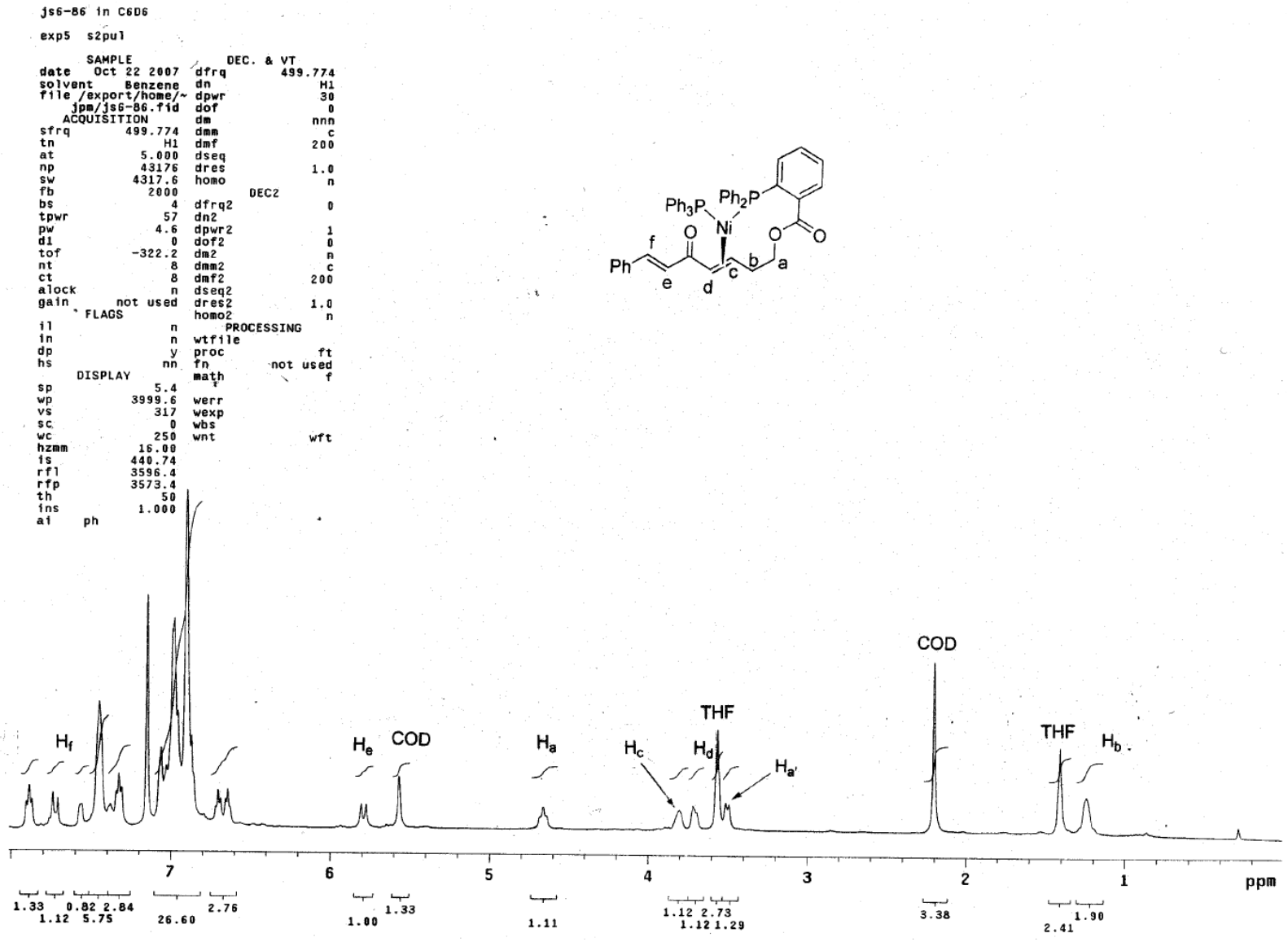
(*E*)-5-Oxo-7-phenyldeca-3,9-dienyl benzoate (2.220). An oil. R_f = 0.17 (SiO_2, 6:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3071 (m), 3025 (m), 2919 (m), 2851 (m), 1720 (s), 1673 (s), 1636 (s), 1454 (m), 1272 (s), 1104 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.96-8.04 (2H, m), 7.52-7.58 (1H, m), 7.38-7.46 (2H, m), 7.18-7.27 (2H, m), 7.10-7.18 (3H, m), 6.74 (1H, dt, J = 16 Hz, *J* = 6.8 Hz), 6.12 (1H, dt, *J* = 16 Hz, *J* = 2 Hz), 5.61 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 6.8 Hz), 4.86-5.00 (2H, m), 4.37 (2H, t, *J* = 6.4 Hz), 3.27 (1H, p, *J* = 7.2 Hz), 2.85 (1H, dd, *J* = 17 Hz, *J* = 6.4 Hz), 2.82 (1H, dd, *J* = 17 Hz, *J* = 7.6 Hz), 2.61 (2H, q, *J* = 6.8 Hz), 2.36 (2H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 198.6, 166.2, 144.0, 141.9, 136.1, 133.0, 132.4, 129.9, 129.5, 128.34, 128.32, 127.4, 126.3, 116.7, 62.71, 46.31, 41.00, 40.62, 31.80. LRMS (ESI+) Calcd for $C_{23}H_{24}O_3$ $(M + H)^+$: 349.2, Found $(M + H)^+$: 349.1.

Synthesis of Ni-enone Complex 2.101



An oven dried 20 mL vial with magnetic stir-bar was charged with 27.5 mg (0.0999 mmol) of bis(1,5-cyclooctadiene)nickel, 49.0 mg (0.0999 mmol) of **2.96**, and 1.0 mL of THF in a dry-box under an argon atmosphere. After stirring for 5 min, a deep purple solution formed, to which was then added 26.2 mg (0.0999 mmol) of triphenylphosphine. This mixture was allowed to stir for an additional 1 h providing a deep red solution. Volatile material was removed under reduced pressure in the dry-box. The residue was triturated with degassed pentane (3x) and dried under vacuum to afford 88.1 mg of a deep red solid.

Complex 2.101. Mp 152-172 ^{o}C (sealed capillary, decomp.). ^{1}H NMR (C_6D_6): δ 7.89 (1H, t, *J* = 8.5 Hz), 7.73 (1H, d, *J* = 16 Hz, H_f), 7.34-7.60 (8H, m), 7.33 (2H, t, *J* = 8.5 Hz). 6.78-7.11 (27H, m), 6.71 (1H, t, *J* = 7.0 Hz), 6.64 (1H, t, *J* = 7.5 Hz), 5.80 (1H, d, *J* = 16 Hz, H_e), 4.66 (1H, br t, H_a), 3.80 (1H, m, H_c), 3.71 (1H, m, H_d), 3.50 (1H, d, *J* = 11 Hz, $H_{a'}$), 1.15-1.32 (2H, m, H_b); ^{13}C NMR (C_6D_6), diagnostic peaks: δ 187.8 (C_g), 168.1, 137.21 (C_f), 130.65 (C_e), 71.15 (C_d, d, $^{2}J_{CP}$ = 11 Hz), 62.52 (C_a), 54.23 (C_c, d, $^{2}J_{CP}$ = 20 Hz), 27.98 (C_b). Note that the aromatic region was too complex for further assignment. ^{31}P NMR (C_6D_6): δ 41.21 (d, $^{2}J_{PP}$ = 32 Hz), 28.59 (d, $^{2}J_{PP}$ = 32 Hz).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date Oct 22 2007
solvent Benzene
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jpm/js6-86.fid
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tn H1
at 5.000
np 43176
sw 4317.6
fb 2000
bs 4
tpwr 57
pw 4.6
d1 0
tof -322.2
nt 8
ct 8
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp 5.4
wp 3999.6
vs 317
sc 0
wc 250
hzmm 16.00
is 440.74
rfl 3596.4
rfp 3573.4
th 50
ins 1.000
ai ph
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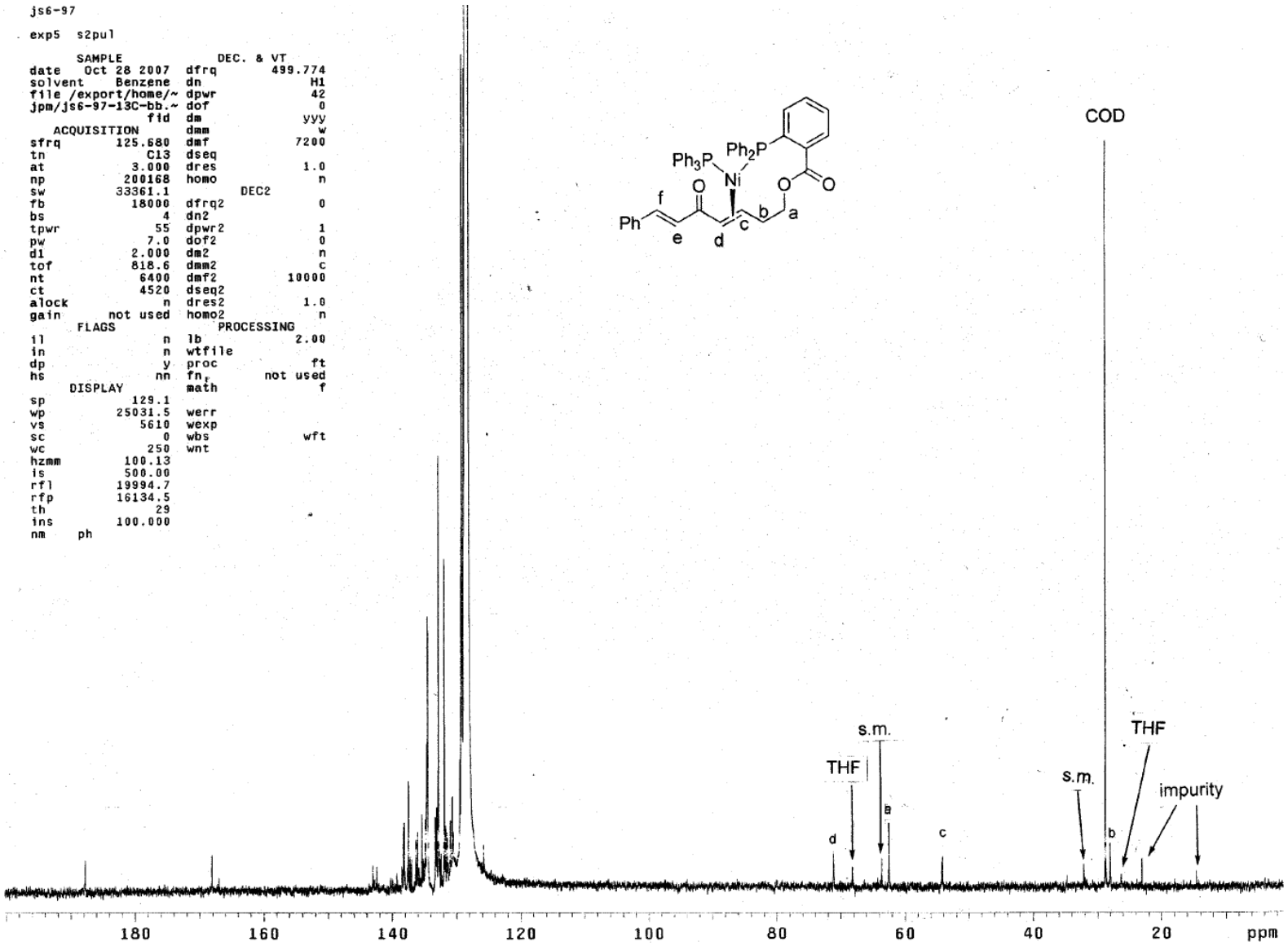
dfrq 499.774
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
PROCESSING
wtfile
proc ft
fn not used
math f
werr
wexp
wbs
wnt wft
Ph3P
Ph2P
Ni
O
O
O
Ph
f
e
d
c
b
a
Hf
He
COD
Ha
Hc
Hd
THF
Ha'
COD
THF
Hb
7
6
5
4
3
2
1
ppm
1.33
0.82
2.84
1.12
5.75
26.60
2.76
1.00
1.33
1.11
1.12
2.73
1.12
1.29
3.38
2.41
1.90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date Oct 28 2007
solvent Benzene
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jpm/js6-97-13C-bb.~
fid
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at 3.000
np 200168
sw 33361.1
fb 18000
bs 4
tpwr 55
pw 7.0
d1 2.000
tof 818.6
nt 6400
ct 4520
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp 129.1
wp 25031.5
vs 5610
sc 0
wc 250
hzmm 100.13
is 500.00
rfl 19994.7
rfp 16134.5
th 29
ins 100.000
nm ph
DEC. & VT
dfrq 499.774
dn H1
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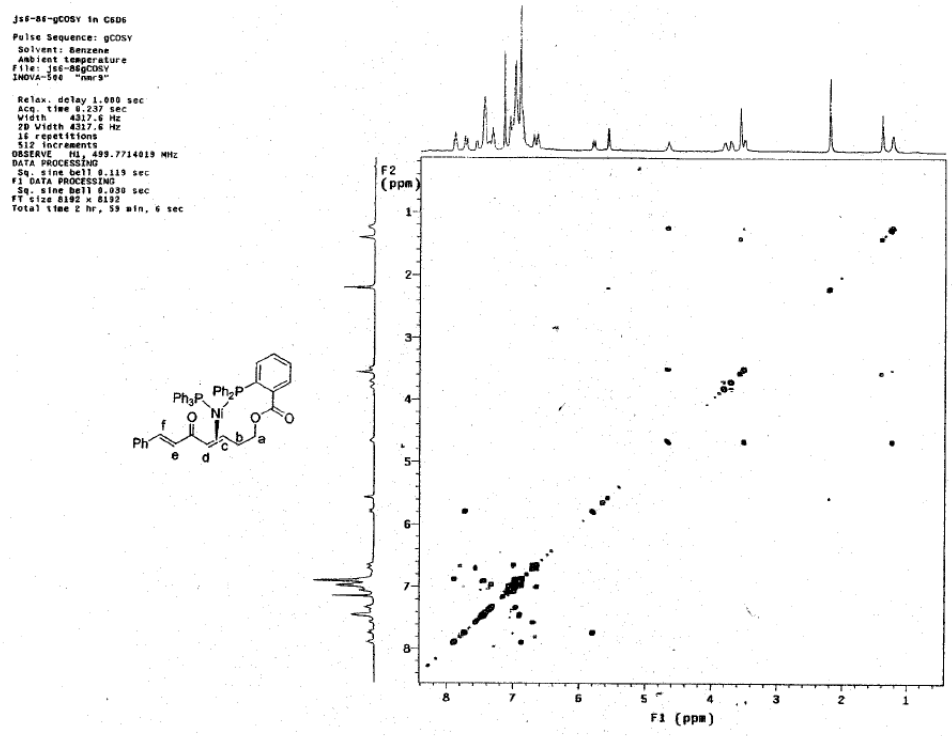
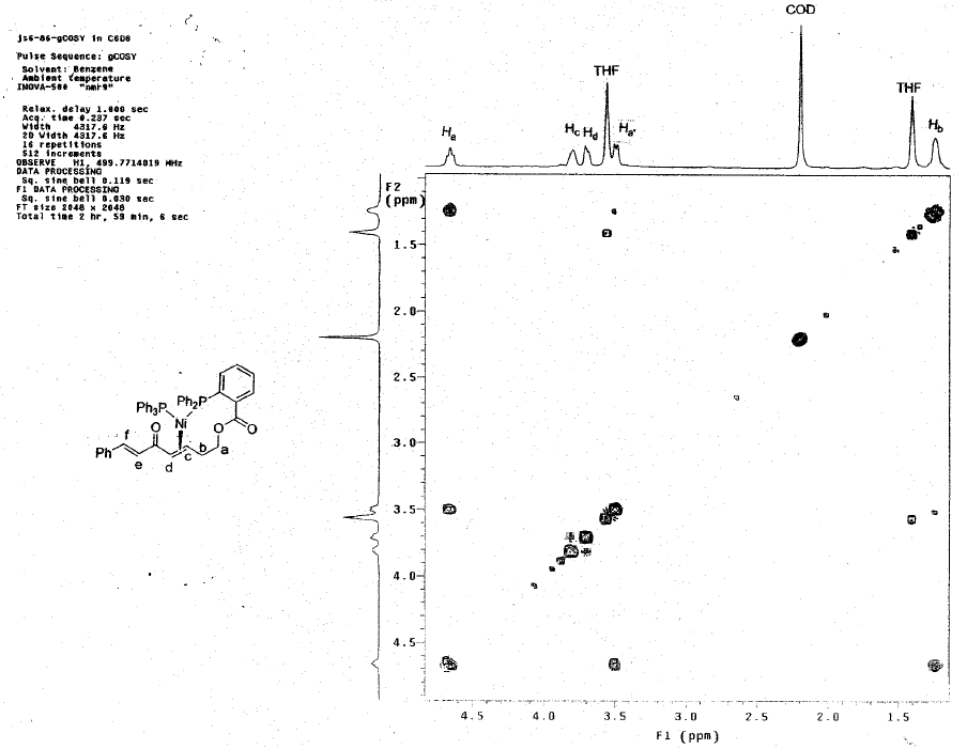
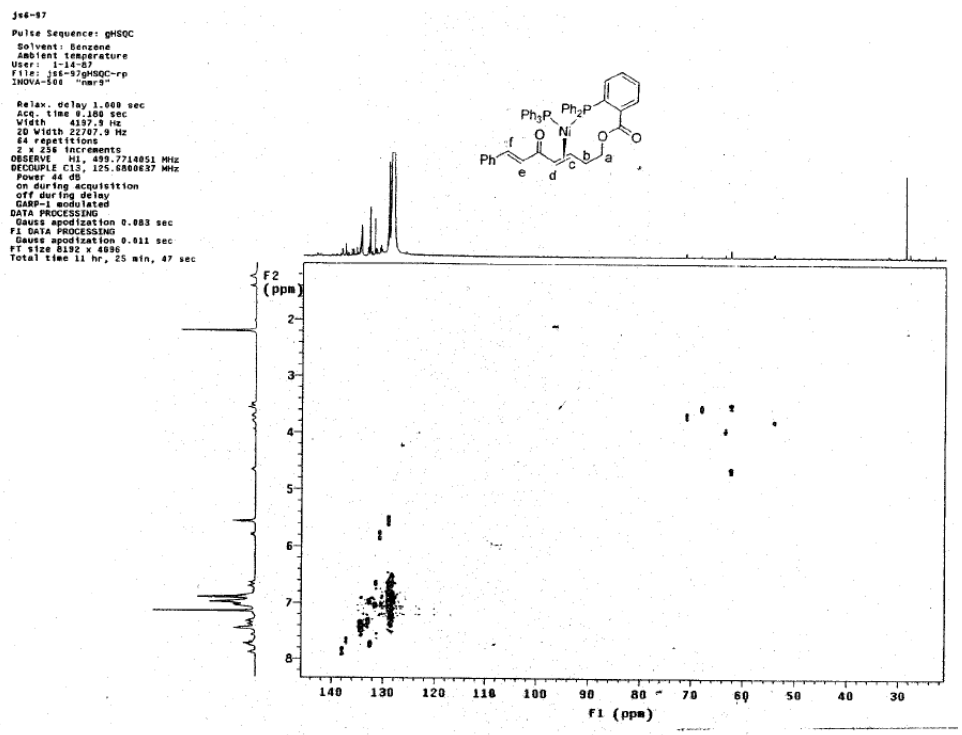
dof 0
dm yyy
dmm w
dmf 7200
dseq
dres 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 10000
dseq2
dres2 1.0
homo2 n
PROCESSING
lb 2.00
wtfile
proc ft
fn not used
math f
werr
wexp
wbs wft
wnt
Ph3P
Ph2P
Ni
O
O
O
Ph
f
e
d
c
b
a
COD
s.m.
THF
s.m.
THF
impurity
d
a
c
b
180
160
140
120
100
80
60
40
20
ppm

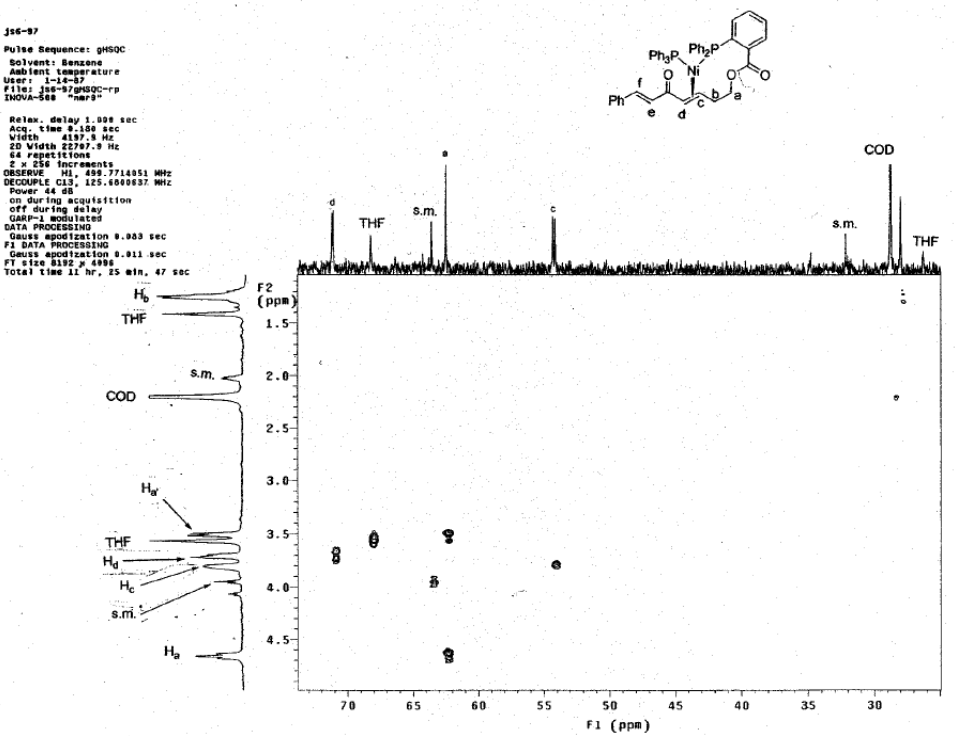
COSY of **2.101** in C_6D_6:



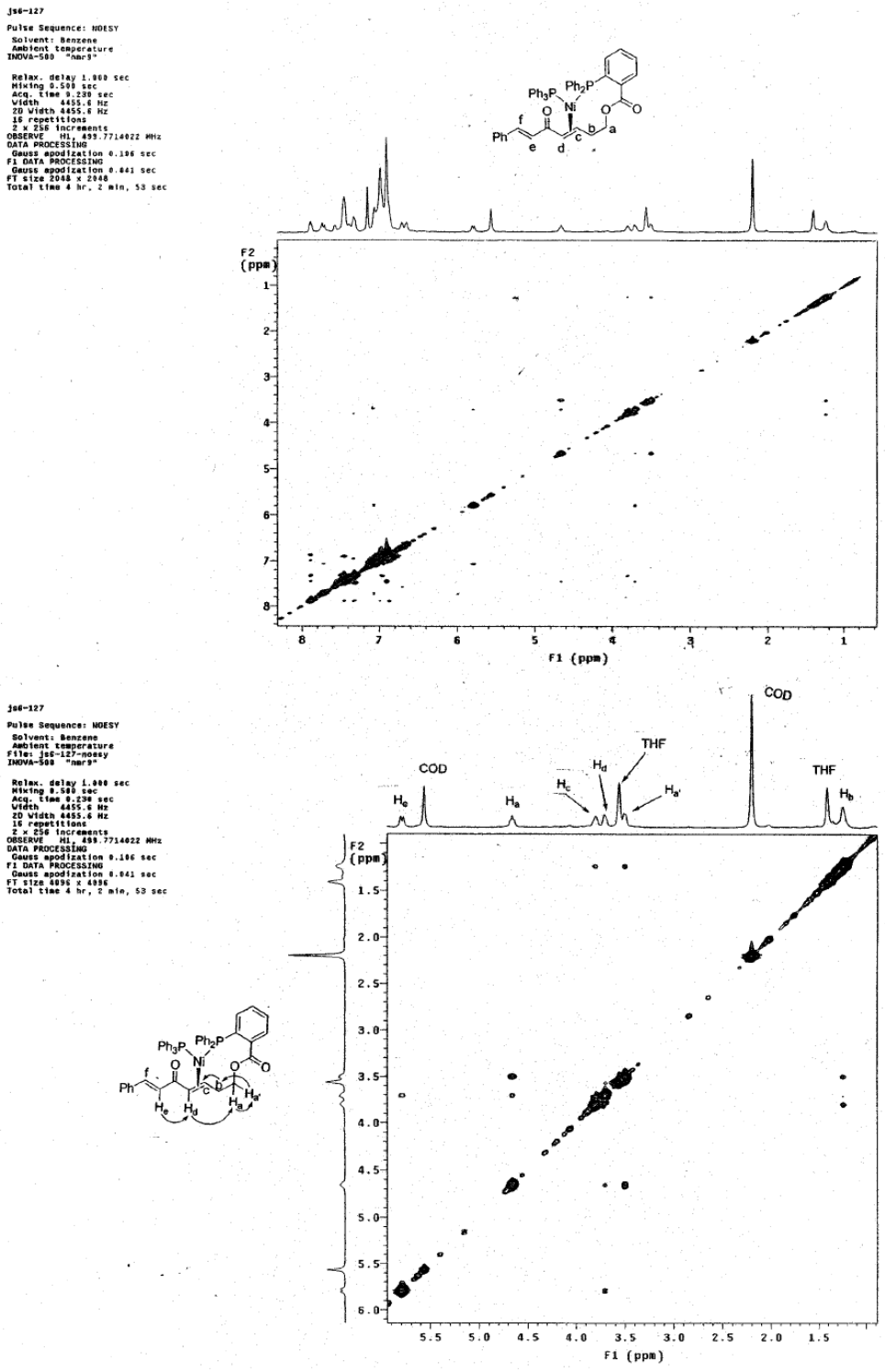


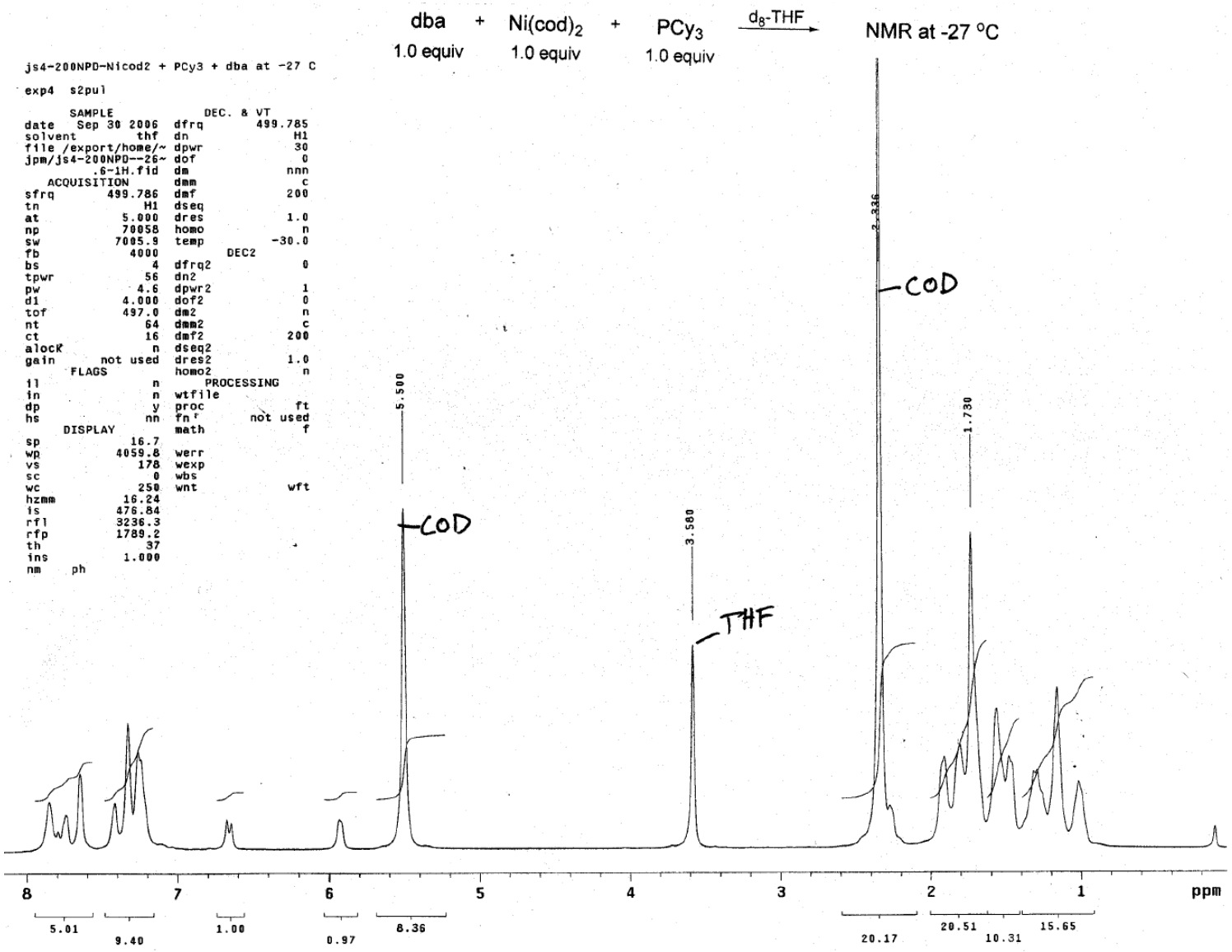
HSQC of **2.101** in C_6D_6:





NOESY of **2.101** in C_6D_6:




dba + Ni(cod)2 + PCy3 d8-THF NMR at -27 °C
1.0 equiv 1.0 equiv 1.0 equiv
js4-200NPD-Nicod2 + PCy3 + dba at -27 C
exp4 s2pul
SAMPLE
date Sep 30 2006
solvent thf
file /export/home/~
jpm/js4-200NPD--26~
.6-1H.fid
ACQUISITION
sfrq 499.786
tn H1
at 5.000
np 70058
sw 7005.9
fb 4000
bs 4
tpwr 56
pw 4.6
d1 4.000
tof 497.0
nt 64
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp 16.7
wp 4059.8
vs 178
sc 0
wc 250
hzmm 16.24
is 476.84
rfl 3236.3
rfp 1789.2
th 37
ins 1.000
nm ph
DEC. & VT
dfrq 499.785
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
temp -30.0
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
PROCESSING
wtfile
proc ft
fn not used
math f
werr
wexp
wbs
wnt wft
5.500
COD
3.580
THF
2.336
COD
1.730
8
7
6
5
4
3
2
1
ppm
5.01
9.40
1.00
0.97
8.36
20.17
20.51
10.31
15.65

Js4-200NPD-Nicod2 + PCy3 + dba at -27C

exp4 s2pul

SAMPLE		DEC. & VT	
date	Sep 30 2006	dfrq	499.785
solvent	thf	dn	H1
file	/export/home/~	dpwr	39
	jpm/js4-200NPD--26~	dof	0
	.6-31P.fid	dm	yyy
ACQUISITION		dmm	w
sfrq	202.312	dmf	11905
tn	P31	dseq	
at	2.000	dres	1.0
np	279966	homo	n
sw	69991.3	temp	-30.0
fb	39000	DEC2	
bs	4	dfrq2	0
tpwr	56	dn2	
pw	15.0	dpwr2	1
d1	1.000	dof2	0
tof	1500.0	dm2	n
nt	128	dmm2	c
ct	48	dmf2	9900
alock	n	dseq2	
gain	not used	dres2	1.0
FLAGS		homo2	n
il	n	PROCESSING	
in	n	lb	2.00
dp	y	wtfile	
hs	ny	prod	ft
DISPLAY		fn	not used
sp	-38987.8	math	f
wp	69991.0		
vs	46	werr	
sc	0	wexp	
wc	250	wbs	
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is	500.00		
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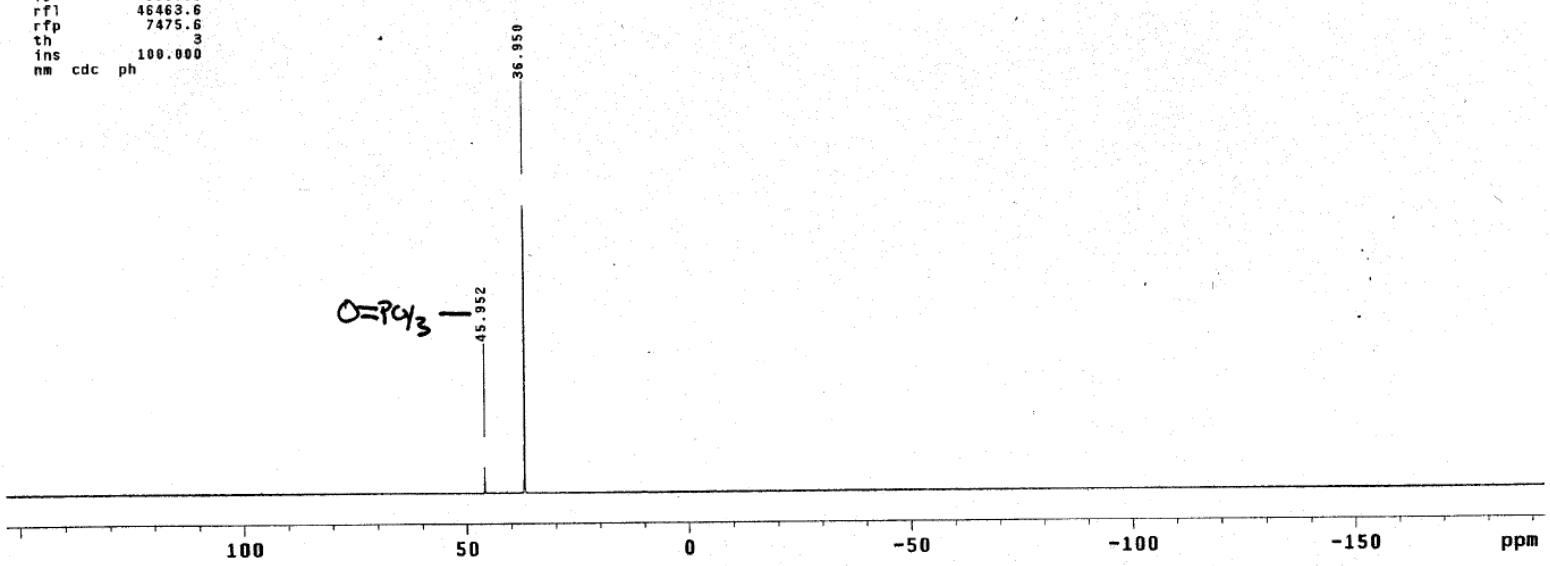
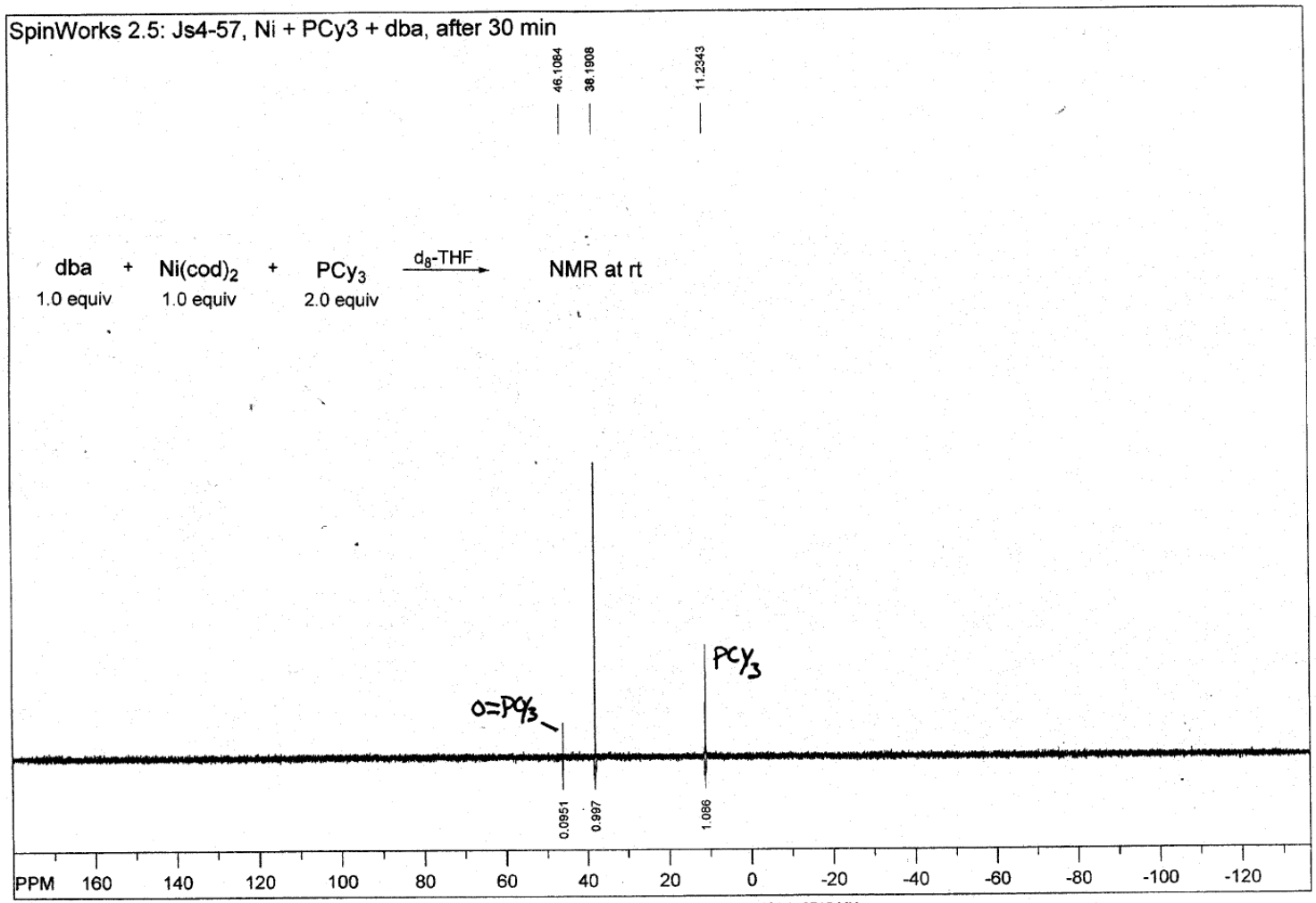
rfp	7475.6		
th	3		
ins	100.000		
nm cdc ph			



dba (1.0 equiv) + $Ni(cod)_2$ (1.0 equiv) + PCy_3 (1.0 equiv) $\xrightarrow{d_8\text{-THF}}$ NMR at -27 °C



file: D:\sieber2\Js4-57\21\fid expt: <zgpg30>
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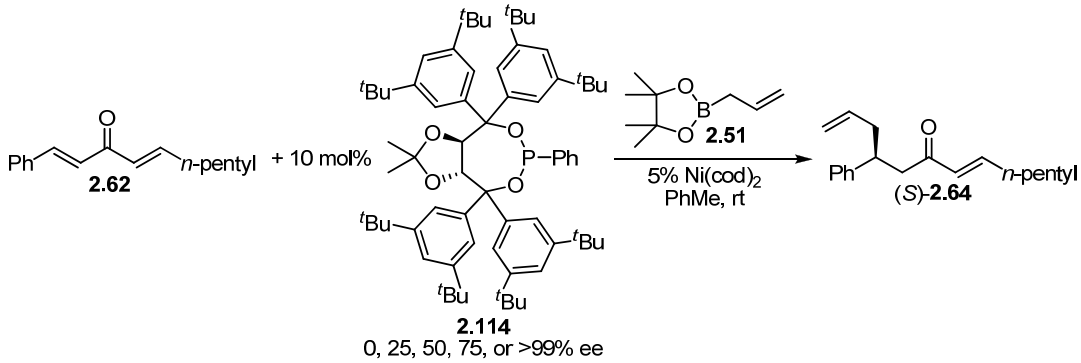
time domain size: 65536 points
width: 51282.05 Hz = 316.660943 ppm = 0.782502 Hz/pt
number of scans: 80

freq. of 0 ppm: 161.942715 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000
Hz/cm: 2051.282 ppm/cm: 12.66644

Non-linear effects (Figures 2.6 and 2.7):

Effect of Ligand Enantiomeric Purity on Enantioselectivity



An oven-dried 2-dram vial, equipped with a magnetic stir-bar, was charged with 3.0 mg (0.011 mmol) of bis(1,5-cyclooctadiene)nickel. The two enantiopodes of ligand **2.114** were then added as 0.100 M stock solutions in toluene, using gas-tight syringes, to make the desired enantiomeric purity of ligand for the reaction (0, 25, 50, and 75 % ee were examined). Next, 221 μL of toluene was added, and this mixture was allowed to stir for 45 min. Next, 44.2 mg (0.263 mmol) of **2.51** was added, followed by 50.0 mg (0.219 mmol) of **2.62**. The vial was capped, sealed with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 20 h. After this time period, degassed water (N_2 sparge) was added, and the mixture transferred to a separatory funnel with CH_2Cl_2. After swirling the layers, the organic layer was collected, and the aqueous layer washed with CH_2Cl_2 (2x). The combined organic layers were dried with anhydrous Na_2SO_4, and volatile material was removed under reduced pressure. Analysis of the unpurified mixture using GLC was used to determine the chemoselectivity of the reaction. Purification using silica gel chromatography (hexanes/EtOAc) afforded the

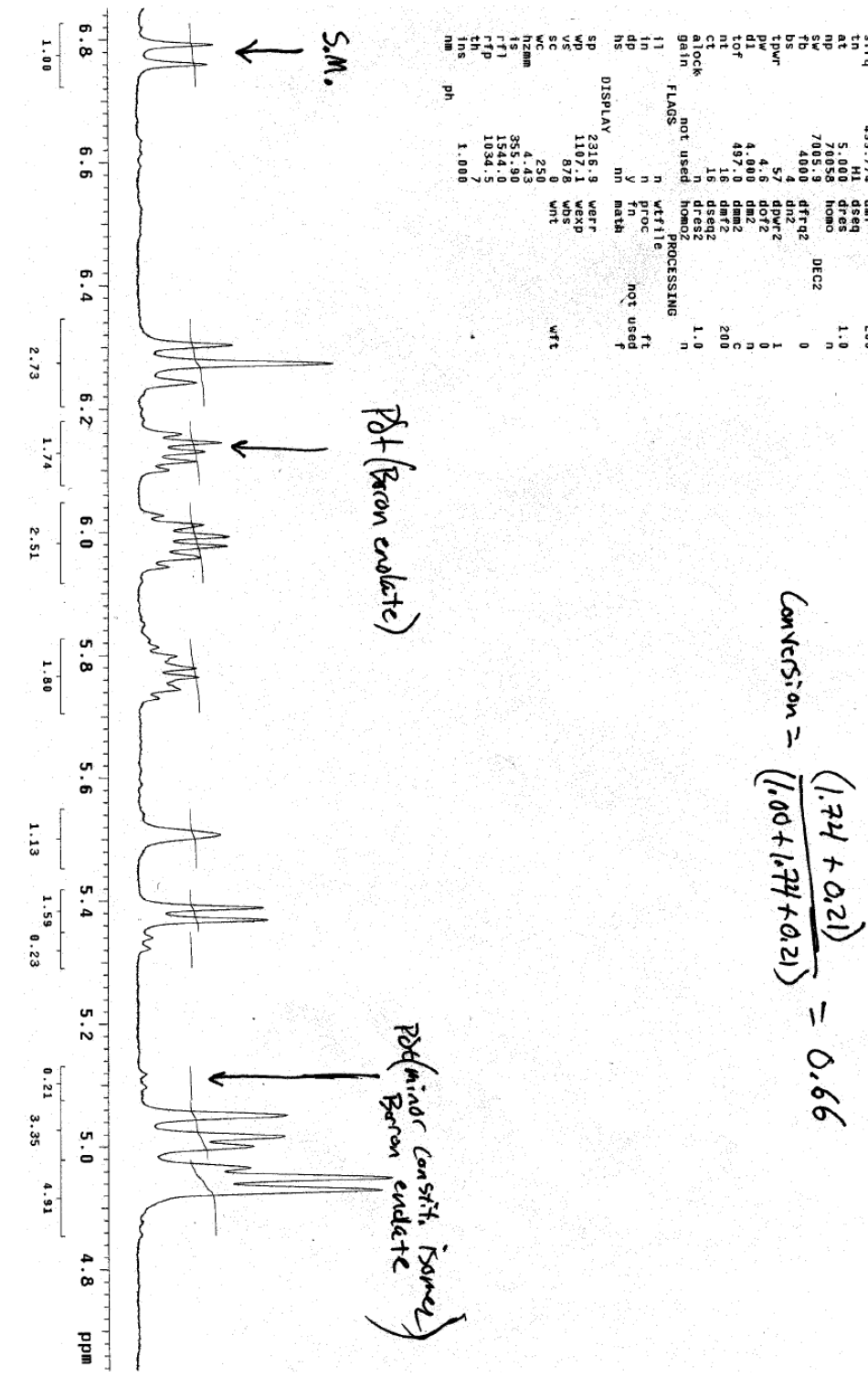
conjugate allylation product. Enantioselectivity was determined by SFC analysis of the purified material.

Effect of Ligand Enantiomeric Purity on Conversion

Enantiomerically pure and racemic catalyst stock solutions, consisting of a mixture of $Ni(cod)_2$ and ligand **2.114**, were prepared using 3.4 mg of $Ni(cod)_2$ and 24.5 mg of enantiomerically pure or racemic ligand **2.114** in 240 μL of toluene-d_8, respectively. The catalyst stock solutions were then allowed to stand at room temperature for 45 min before use. To two oven-dried J-Young NMR tubes, in a dry-box, was added 350 μL of a 0.750 M stock solution of **2.51** in toluene-d_8 to each tube. To one tube was added 175 μL of the enantiomerically pure catalyst stock solution, and to the other tube was added 175 μL of the racemic catalyst solution. Finally, 350 μL of a 0.500 M stock solution of **2.62** in toluene-d_8 was added to each tube, and each tube was capped and inverted several times. The reactions were followed by ^{1}H NMR, and the ratio of starting material to product[1] was used to calculate conversion. After complete consumption of starting material, the reactions were worked up as described for the general procedure for the Ni-catalyzed asymmetric conjugate allylation of **2.62** on page 257.

[1] Note that the product observed during the reaction was the expected intermediate boron enolate.

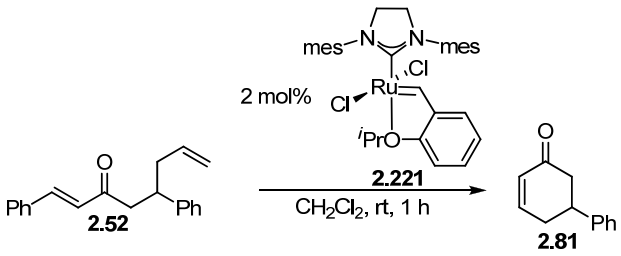
Sample ^{1}H NMR spectrum for conversion calculation:



$$\text{Conversion} = \frac{(1.74 + 0.21)}{(1.00 + 1.74 + 0.21)} = 0.66$$

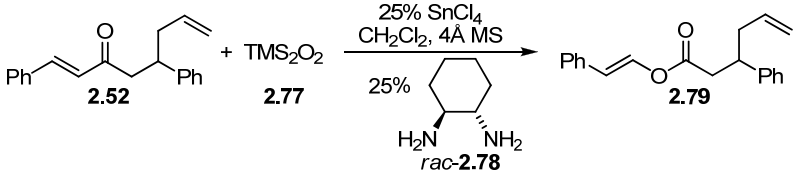
6. Synthetic Transformations

Synthesis of 2.81



To 47.9 mg (0.173 mmol) of **2.52** was added 2.2 mg (0.0035 mmol) of the Hoveyda-Grubbs' 2nd generation catalyst (**2.221**) in a dry-box under an argon atmosphere. This mixture was then diluted with 5.7 mL of dry, degassed CH_2Cl_2, and a magnetic stir-bar was added. A septum was fitted on the reaction flask, and the reaction was removed from the dry-box and allowed to stir at room temperature under N_2. After 1 h, 3 drops (22 gauge needle) of *t*-butyl vinyl ether was added, and volatile material was removed under reduced pressure. Silica gel chromatography (pentane/Et_2O) of the mixture afforded 28.1 mg (0.163 mmol, 94%) of 5-phenylcyclohex-2-enone (**2.81**). Spectral data were consistent with the literature.[1]

Synthesis of 2.79



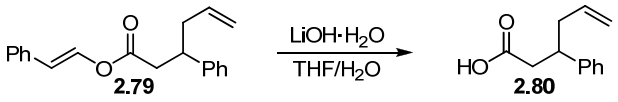
[1] Rutherford, A. P.; Gibb, C. S.; Hartley, R. C.; Goodman, J. M. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1051.

In a 2-dram vial with magnetic stir-bar, in a dry-box under Ar, was weighed ~30 mg of crushed 4 Å molecular sieves. Next, 33.8 μL (0.034 mmol) of a 1.0 M solution of (±)-*trans*-1,2-diaminocyclohexane (**2.78**) in CH_2Cl_2 was added by syringe, followed by dilution with 0.32 mL of CH_2Cl_2. Next, 33.8 μL (0.034 mmol) of a 1.0 M solution of $SnCl_4$ in CH_2Cl_2 was added, and the vial was capped with a septum, removed from the dry-box, and cooled to 0 ^oC (ice/brine). TMS_2O_2 (**2.77**) was added dropwise as a 1.0 M solution in CH_2Cl_2 (0.27 mL, 0.27 mmol). The mixture was allowed to stir for 10 min at this temperature, and then, 37.3 mg (0.135 mmol) of **2.52** was added in 0.59 mL of CH_2Cl_2 by canula. The reaction became a blue-gray color and was subsequently warmed to room temperature and allowed to stir for 15 h. Sodium sulfite (41 mg) was then added, and the reaction was allowed to stir for an additional 3 h. Finally, the reaction was filtered through a pad of silica gel using EtOAc and concentrated under reduced pressure. Silica gel chromatography (hexanes/EtOAc) of the mixture afforded 31.5 mg (0.108 mmol, 80 %) of **2.79** as a white solid.

(*E*)-Styryl-3-phenylhex-5-enoate (2.79). Mp = 66-70^oC. R_f = 0.24 (30:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 3087 (m), 3024 (m), 2917 (m), 1747 (s), 1652 (m), 1495 (m), 1212 (m), 1142 (s) cm^{-1}; ^1H NMR: δ 7.74 (1H, d, *J* = 13 Hz), 7.24-7.39 (6H, m), 7.10-7.24 (4H, m), 6.03 (1H, d, *J* = 13 Hz), 5.66 (1H, m), 5.02 (2H, m), 3.26 (1H, p, *J* = 7.2 Hz), 2.81 (1H, dd, *J* = 16 Hz, *J* = 6.4 Hz), 2.68 (1H, dd, *J* = 16 Hz, *J* = 8.4 Hz), 2.42 (2H, m); ^{13}C NMR: δ 169.3, 143.1, 136.1, 135.6, 134.0, 128.6, 128.5, 127.3,

126.7, 126.1, 117.1, 115.2, 41.56, 40.61, 40.26. LRMS (ESI+) Calcd for $C_{20}H_{20}O_2$ (M + Na)$^+$: 315, Found (M + Na)$^+$: 315.

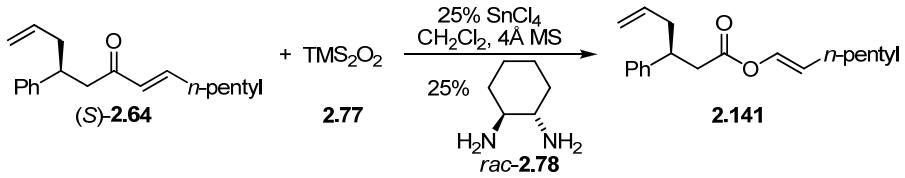
Synthesis of 2.80



To a solution of 26.3 mg (0.900 mmol) of **2.79** in 0.68 mL of THF was added 0.22 mL of water, and the reaction was subsequently cooled to 0 ^oC. LiOH•H_2O (7.6 mg, 0.18 mmol) was then added, and the reaction was allowed to stir at this temperature and monitored by TLC. After complete consumption of the starting material (2-2.5 h), the reaction was acidified with 1 M HCl and extracted with EtOAc (3x). The organic layers were combined, washed with brine, and dried over anhydrous Na_2SO_4. Volatile material was removed under reduced pressure, and the product was purified by silica gel chromatography (1% AcOH in CH_2Cl_2/Et_2O, R_f = 0.25 in 1% AcOH in 20:1 CH_2Cl_2:Et_2O) to give 16.5 mg (0.867 mmol, 96%) of **2.80** after removal of AcOH by azeotropic distillation with toluene using a rotary evaporator followed by removal of toluene via azeotropic distillation with CH_2Cl_2. Spectral data were consistent with the literature.[2]

[2] Allin, S. M.; Essat, M.; Pita, C. H.; Baird, R. D.; McKee, V.; Elsegood, M.; Edgar, M.; Andrews, D. M.; Shah, P.; Aspinall, I. *Org. Biomol. Chem.* **2005**, *3*, 809.

Synthesis of 2.141

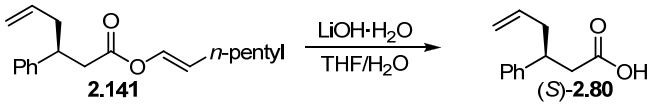


In a 2-dram vial with magnetic stir-bar, in a dry-box under Ar, was weighed ~45 mg of crushed 4 Å molecular sieves. Next, 48.8 μL (0.049 mmol) of a 1.0 M solution of (±)-*trans*-1,2-diaminocyclohexane (**2.78**) in CH_2Cl_2 was added by syringe followed by dilution with 0.43 mL of CH_2Cl_2. Next, 48.8 μL (0.049 mmol) of a 1.0 M solution of $SnCl_4$ in CH_2Cl_2 was added, and the vial was capped with a septum, removed from the dry-box, and cooled to 0 ^oC (ice/brine). TMS_2O_2 (**2.77**) was added dropwise as a 1.0 M solution in CH_2Cl_2 (0.39 mL, 0.39 mmol). The mixture was allowed to stir for 10 min at this temperature, and then, 52.8 mg (0.195 mmol) of (*S*)-**2.64** was added in 0.85 mL of CH_2Cl_2 by canula. The reaction was subsequently warmed to room temperature and allowed to stir for 15 h. Sodium sulfite (60 mg) was then added, and the reaction was allowed to stir for an additional 3 h. Finally, the mixture was filtered through a pad of silica gel using EtOAc and concentrated under reduced pressure. Silica gel chromatography (hexanes/EtOAc) of the mixture afforded 37.8 mg (0.132 mmol, 68 %, 92% brsm) of **2.141** as a colorless oil along with 13.8 mg (0.0510 mmol) of unreacted (*S*)-**2.64**.

(*S,E*)-Hept-1-enyl-3-phenylhex-5-enoate (2.141). R_f = 0.30 (30:1 hexanes:EtOAc); IR (neat): 3080 (m), 3029 (m), 2958 (s), 2928 (s), 2856 (s), 1945 (w), 1750 (s), 1675 (m),

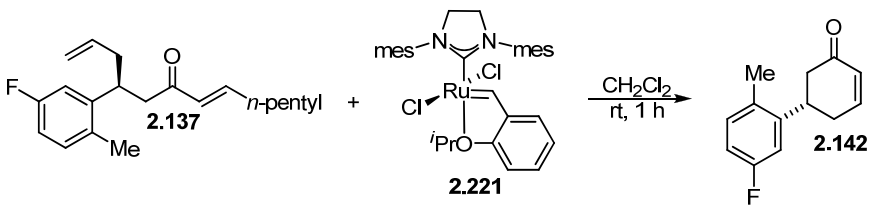
1447 (m), 1236 (m), 1160 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.25-7.32 (2H, m), 77.15-7.23 (3H, m), 6.95 (1H, dt, *J* = 12 Hz, *J* = 2 Hz), 5.64 (1H, ddt, *J* = 17 Hz, *J* = 10 Hz, *J* = 7.2 Hz), 5.33 (1H, dt, *J* = 12 Hz, *J* = 7.2 Hz), 4.91-5.05 (2H, m), 3.22 (1H, p, J = 7.6 Hz), 2.74 (1H, dd, *J* = 16 Hz, *J* = 6.8 Hz), 2.61 (1H, dd, *J* = 16 Hz, *J* = 8.4 Hz), 2.32-2.48 (2H, m), 1.93 (2H, q, *J* = 6.8 Hz), 1.17-1.39 (6H, m), 0.87 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 169.5, 143.3, 135.7, 135.2, 128.4, 127.3, 126.6, 117.0, 115.1, 41.55, 40.55, 40.28, 31.24, 27.16, 27.21, 22.45, 14.02. LRMS (ESI+) Calcd for $C_{19}H_{26}O_2$ $(M + H)^+$: 287.2, Found $(M + H)^+$: 287.1. $[\alpha]_D^{20} = +15^o$ (*c* = 3.0, $CHCl_3$).

Synthesis of (*S*)-2.80



To a solution of 27.4 mg (0.0957 mmol) of **2.141** in 0.96 mL of a 3:1 THF:H_2O mixture at 0 ^oC was added LiOH•H_2O (8.0 mg, 0.19 mmol). The reaction was allowed to reach ambient temperature and allowed to stir for 20h. The reaction was acidified with 1 M HCl and extracted with EtOAc (3x). The organic layers were combined, washed with brine, and dried over anhydrous Na_2SO_4. Volatile material was removed under reduced pressure, and the product was purified using silica gel chromatography (1% AcOH in CH_2Cl_2/Et_2O, R_f = 0.25 in 1% AcOH in 20:1 CH_2Cl_2:Et_2O) to give 17.9 mg (0.0941 mmol, 98%) of (*S*)-**2.80** after removal of AcOH by azeotropic distillation with toluene using a rotary evaporator, followed by removal of toluene via azeotropic distillation with CH_2Cl_2.

Synthesis of 2.142



To 237 mg (0.759 mmol) of **2.137** in a 20 mL scintillation vial with magnetic stir-bar, in a dry-box under an Ar atmosphere, was added a solution of 9.8 mg (0.0157 mmol) of the Hoveyda-Grubbs' second generation catalyst (**2.221**) in 16 mL of CH_2Cl_2. The vial was capped, sealed with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 1 h. Next, 0.15 mL of *t*-butyl vinyl ether was added, and the mixture was allowed to stir for another 30 min. The reaction was concentrated under reduced pressure and purified using column chromatography (SiO_2, pentane:Et_2O) to afford 152 mg (0.743 mmol, 98%) of **2.142** as a colorless oil.

(*R*)-5-(5-Fluoro-2-methylphenyl)cyclohex-2-enone (2.142). R_f = 0.14 (SiO_2, 7:1 pentane:Et_2O); IR (neat): 3031 (m), 2930 (m), 1879 (w), 1678 (s), 1615 (m), 1584 (m), 1495 (s), 1388 (s), 1243 (s), 1161 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.09 (1H, dd, *J* = 8.4 Hz, *J* = 6.0 Hz), 6.99-7.07 (1H, m), 6.91 (1H, dd, *J* = 10 Hz, *J* = 2.8 Hz), 6.81 (1H, dt, *J* = 8.0 Hz, *J* = 2.8 Hz), 6.01 (1H, dd, *J* = 11 Hz, *J* = 2.8 Hz), 3.45-3.58 (1H, m), 2.38-2.62 (4H, m); ^{13}C NMR ($CDCl_3$): δ 198.6, 161.4 (d, $^1J_{CF}$ = 242 Hz), 149.2, 143.0 (d, $^3J_{CF}$ = 6.2 Hz), 131.9 (d, $^3J_{CF}$ = 7.8 Hz), 130.6, 129.6, 113.2 (d, $^2J_{CF}$ = 21 Hz), 112.3 (d, $^2J_{CF}$ = 21 Hz), 44.16, 36.85, 32.48, 18.50; ^{19}F NMR: δ 95.10 (m). LRMS (APPI) Calcd for $C_{13}H_{13}FO$ $(M + H)^+$: 205.1, Found $(M + H)^+$: 205.1.

```
js5-i55column

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tn               H1 dmm               c
at            3.000 dmf             200
np            35992     PROCESSING
sw           5998.8 wtfile
fb             3400 proc             ft
bs                4 fn         not used
tpwr             63
pw              7.1 werr
d1            4.000 wexp
tof               0 wbs
nt                8 wnt
ct                8
alock             n
gain      not used
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il                n
in                n
dp                y
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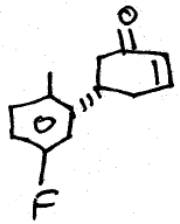

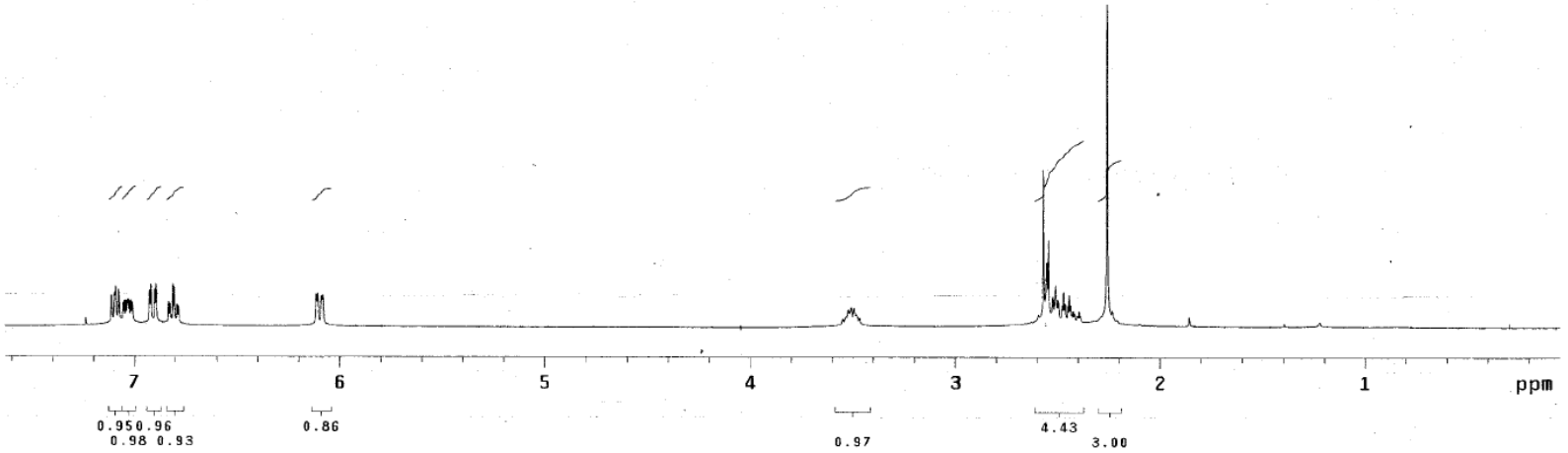

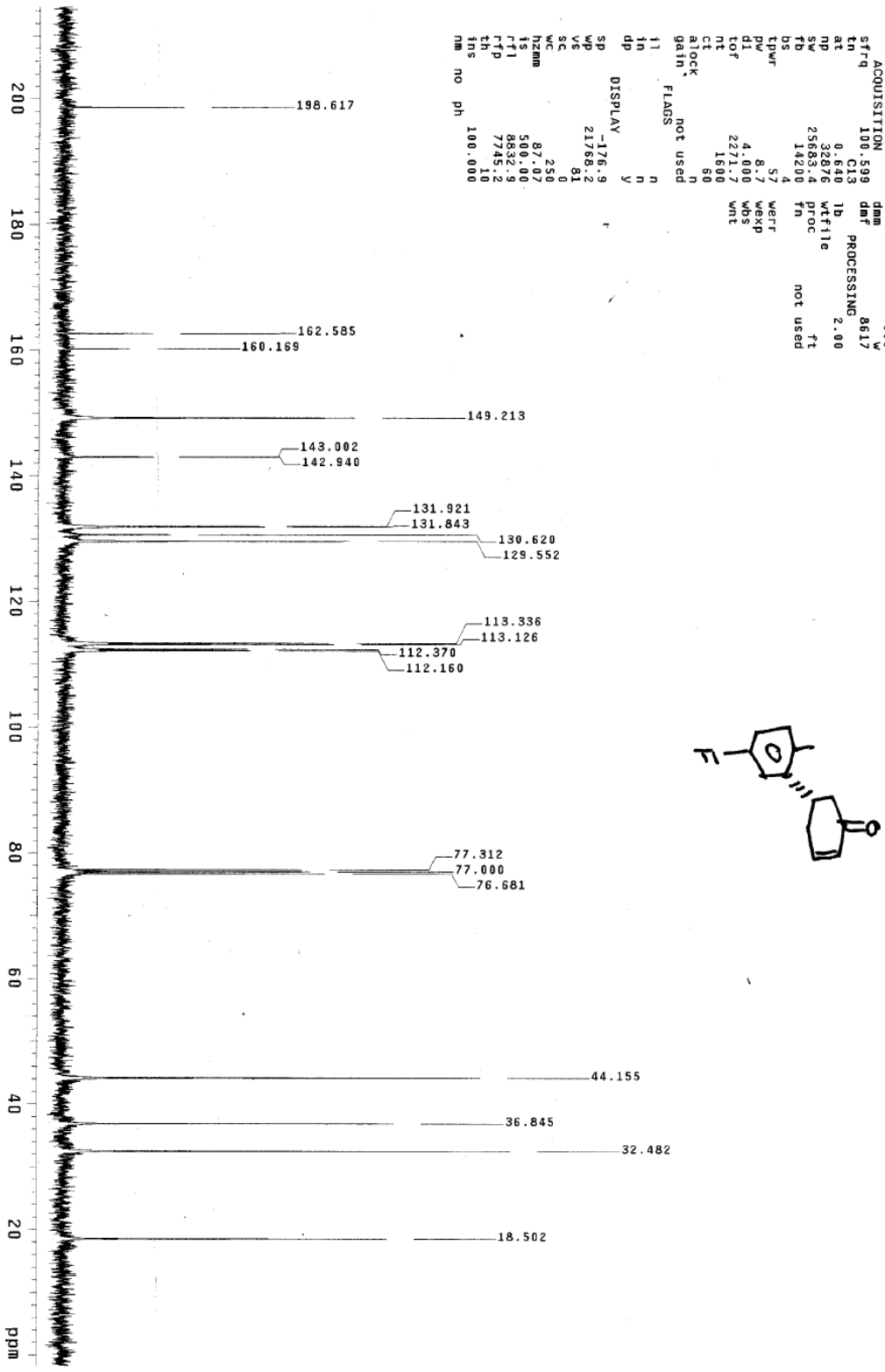
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ct 60
alock n
gain n
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in n
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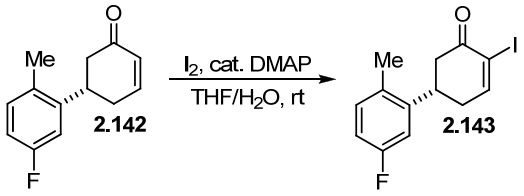
Synthesis of 2.143



To 76.4 mg (0.374 mmol) of **2.142** in a 20 mL scintillation vial with magnetic stir-bar was added 1.9 mL of a 1:1 mixture of THF and H_2O. Next, 142 mg (0.561 mmol) of I_2 was added, followed by 62.1 mg (0.449 mmol) of K_2CO_3. 9.1 mg (0.0748 mmol) of 4-(dimethylamino)pyridine (DMAP) was added, and the vial was purged with N_2, capped, and allowed to stir at ambient temperature while monitoring the reaction by TLC. After 2 h, starting material had been consumed, so the mixture was transferred to a separatory funnel with EtOAc and washed with saturated aqueous $Na_2S_2O_3$. The organic layer was washed with 11 mL of 0.1 M HCl, and then, dried with anhydrous Na_2SO_4. Volatile material was removed under reduced pressure, and 112 mg (0.339 mmol, 91%) of **2.143** was isolated, as a white solid, after purification by silica gel chromatography (hexanes:EtOAc).

(*S*)-5-(5-Fluoro-2-methylphenyl)-2-iodocyclohex-2-enone (2.143). Mp 100-106 ^{o}C. R_f = 0.23 (SiO_2, 10:1 hexanes:EtOAc); IR (CH_2Cl_2 solution): 2930 (m), 1684 (s), 1615 (m), 1590 (m), 1495 (s), 1318 (m), 1250 (m) cm^{-1}; ^{1}H NMR: δ 7.79 (1H, t, J = 4.4 Hz), 7.11 (1H, dd, J = 8.4 Hz, J = 6.0 Hz), 6.89 (1H, dd, J = 10 Hz, J = 2.8 Hz), 6.83 (1H, dt, J = 8.4 Hz, J = 2.8 Hz), 3.59 (1H, m), 2.86 (1H, dd, J = 16 Hz, J = 3.6 Hz), 2.72 (1H, dd, J = 16 Hz, J = 14 Hz) 2.50-2.64 (2H, m), 2.26 (3H, s); ^{13}C NMR: δ 191.4, 161.4 (d, $^{1}J_{CF}$ =

242 Hz), 157.8, 141.8 (d, $^{3}J_{CF}$ = 6.2 Hz), 132.1 (d, $^{3}J_{CF}$ = 7.8 Hz), 130.7, 113.6 (d, $^{2}J_{CF}$ = 21 Hz), 112.2 (d, $^{2}J_{CF}$ = 22 Hz), 103.4, 43.09, 36.89, 36.47, 18.56; ^{19}F NMR: δ 95.43 (m). LRMS (APPI) Calcd for $C_{13}H_{12}FIO$ $(M + H)^{+}$: 331.0, Found $(M + H)^{+}$: 331.0.

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js5-111column

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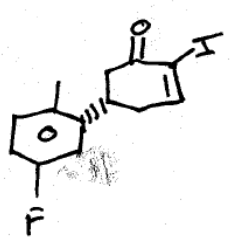

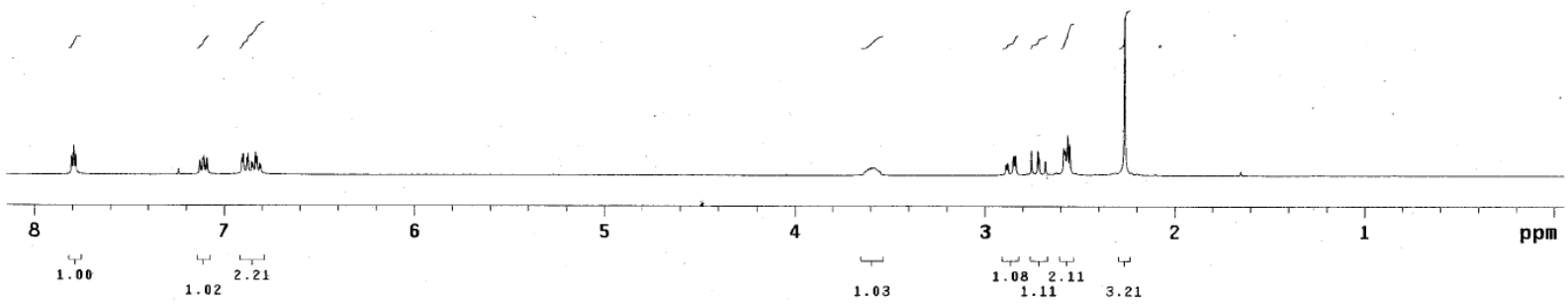

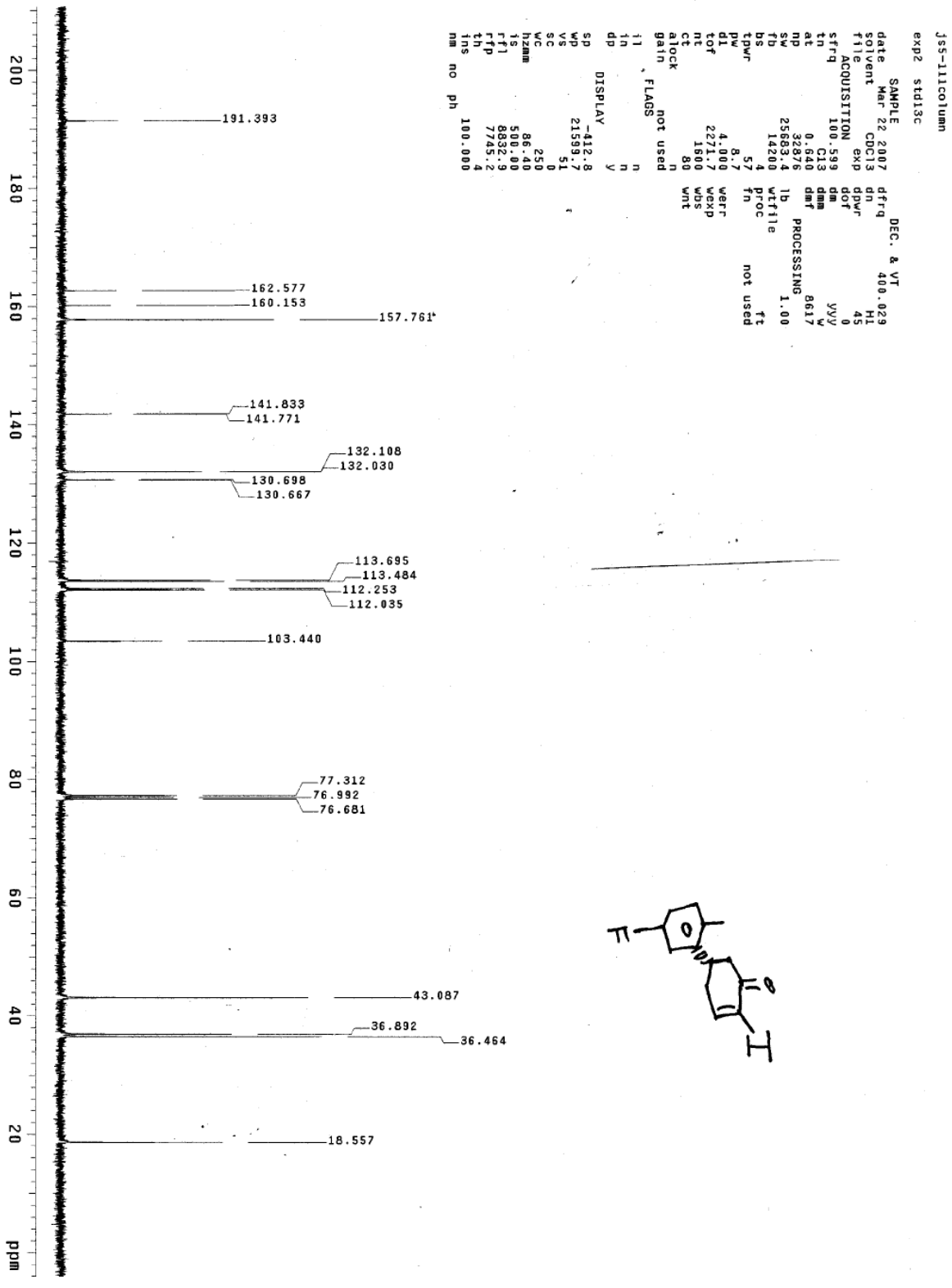
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gain not used
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dp y
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ft
proc
fn
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160.153
157.761
141.833
141.771
132.108
132.030
130.698
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113.695
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76.681
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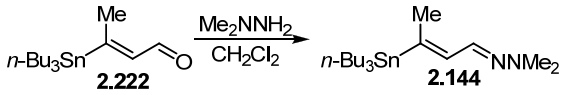
Synthesis of 2.144

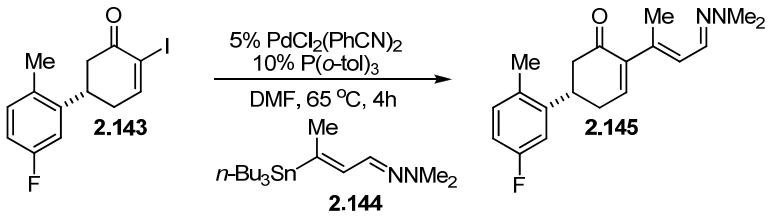


To a mixture of 1.93 g (5.37 mmol) of **2.222**[1] and 1.29 g (10.7 mmol) of $MgSO_4$, in 18 mL of CH_2Cl_2 at 0 ^oC under N_2, was added 0.41 mL (5.4 mmol) of dimethylhydrazine, dropwise. After complete addition, the reaction was warmed to room temperature and allowed to stir for 2 h. The mixture was filtered through celite and concentrated under reduced pressure. Column chromatography (neutral alumina, hexanes:EtOAc) afforded 1.81 g (4.51 mmol, 84%) of **2.144** as a slight yellow oil.

(*E*)-1,1-Dimethyl-2-[3-(tributylstannyl)-but-2-enylidene]hydrazine (2.144). R_f = 0.26 (Al_2O_3, 40:1 hexanes:EtOAc); IR (neat): 2961 (s), 2930 (s), 2848 (s), 1860 (w), 1595 (m), 1551 (m), 1469 (m), 1356 (m), 1274 (m), 1129 (m) cm^{-1}; ^1H NMR: δ 7.31 (1H, d, *J* = 8.8 Hz), 6.30 (1H, dq, *J* = 8.8 Hz, *J* = 1.6 Hz, $^3J_{SnH}$ = 67.2 Hz), 2.85 (6H, s), 2.03 (3H, d, *J* = 2 Hz, $^3J_{SnH}$ = 45.2 Hz), 1.34-1.58 (6H, m), 1.28 (6H, h, *J* = 7.2 Hz) 0.78-1.01 (15H, m); ^{13}C NMR: δ 144.1, 136.8, 131.7, 42.90, 29.15, 27.41, 19.96, 13.72, 9.21. LRMS (APPI) Calcd for $C_{18}H_{38}N_2Sn$ $(M + H)^+$: 403.2, Found $(M + H)^+$: 403.2.

[1] Lipshutz, B. H.; Clososki, G. C.; Chrisman, W.; Chung, D. W.; Ball, D. B.; Howell, J. *Org. Lett.* **2005**, *7*, 4561.

Synthesis of 2.145



To an oven-dried 2-dram vial with magnetic stir-bar, in a dry-box under an Ar atmosphere, was weighed 1.7 mg (0.0046 mmol) of bis(benzonitrile)palladium dichloride, 2.8 mg (0.0091 mmol) of tri-*o*-tolylphosphine, and 30.0 mg (0.0909 mmol) of **2.143**. Next, 0.43 mL of dry, degassed *N*,*N*-dimethylformamide (DMF) was added, followed by 43.8 mg (0.109 mmol) of **2.144**. The vial was capped, sealed with electrical tape, removed from the dry-box, and heated at 65 ^{o}C for 4 h. After cooling to room temperature, the mixture was diluted with Et_2O and washed with 3 % aqueous KF (2x). The combined aqueous layers were back extracted with Et_2O (1x), and the combined organic layers were dried with anhydrous Na_2SO_4. After removal of volatile material under reduced pressure, 20.9 mg (0.0665 mmol, 73%) of **2.145** was isolated as a yellow solid after purification by silica gel chromatography (first column with hexanes:EtOAc, followed by a second column using CH_2Cl_2:Et_2O).

(*S*)-2-[(2*E*)-4-(2,2-Dimethylhydrazono)but-2-en-2-yl]-5-(5-fluoro-2-methylphenyl)cyclohex-2-enone (2.145). Mp 119-122 ^{o}C. R_f = 0.23 (SiO_2, 2:1 hexanes:EtOAc) and 0.31 (SiO_2, 10:1 CH_2Cl_2:EtOAc); IR (CH_2Cl_2 solution): 2949 (m), 2867 (m), 2779 (w), 1677 (s), 1614 (m), 1551 (m), 1495 (m), 1463 (m), 1343 (m) cm^{-1}; ^{1}H NMR: δ 7.16 (1H, d, J = 9.4 Hz), 7.09 (1H, dd, J = 8.4 Hz, J = 6.4 Hz), 6.91 (1H, dd,

J = 10 Hz, *J* = 4.0 Hz), 6.87 (1H, dd, *J* = 6.0 Hz, *J* = 2.8 Hz), 6.80 (1H, dt, *J* = 8.4 Hz, *J* = 2.8 Hz), 6.25 (1H, d, *J* = 9.4 Hz), 3.48 (1H, m), 2.87 (6H, s), 2.40-2.67 (4H, m), 2.27 (3H, s), 1.99 (3H, s); ^{13}C NMR: δ 197.4, 161.4 (d, $^{1}J_{CF}$ = 242 Hz), 143.7, 143.4, 143.0 (d, $^{3}J_{CF}$ = 6.3 Hz), 133.8, 131.9, 131.8 (d, $^{3}J_{CF}$ = 9.3 Hz), 130.7, 127.4, 113.2 (d, $^{2}J_{CF}$ = 20 Hz), 112.2 (d, $^{2}J_{CF}$ = 22 Hz), 45.18, 42.73, 42.71, 36.90, 33.04, 18.53, 16.58; ^{19}F NMR: δ 95.02 (m). LRMS (ESI+) Calcd for $C_{19}H_{23}FN_2O$ $(M)^+$: 314.2, Found $(M)^+$: 314.9.

js5-152column

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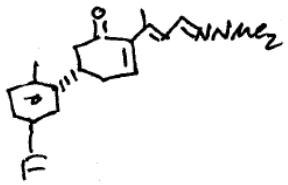

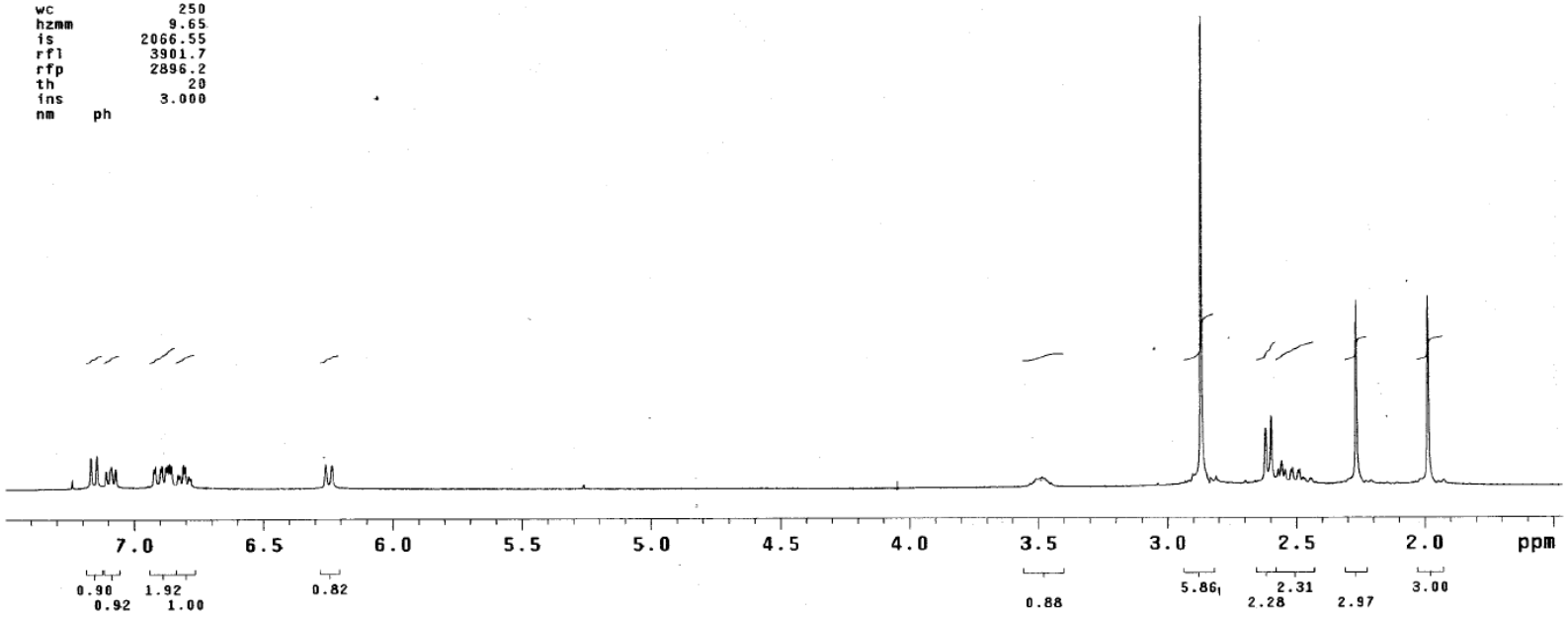

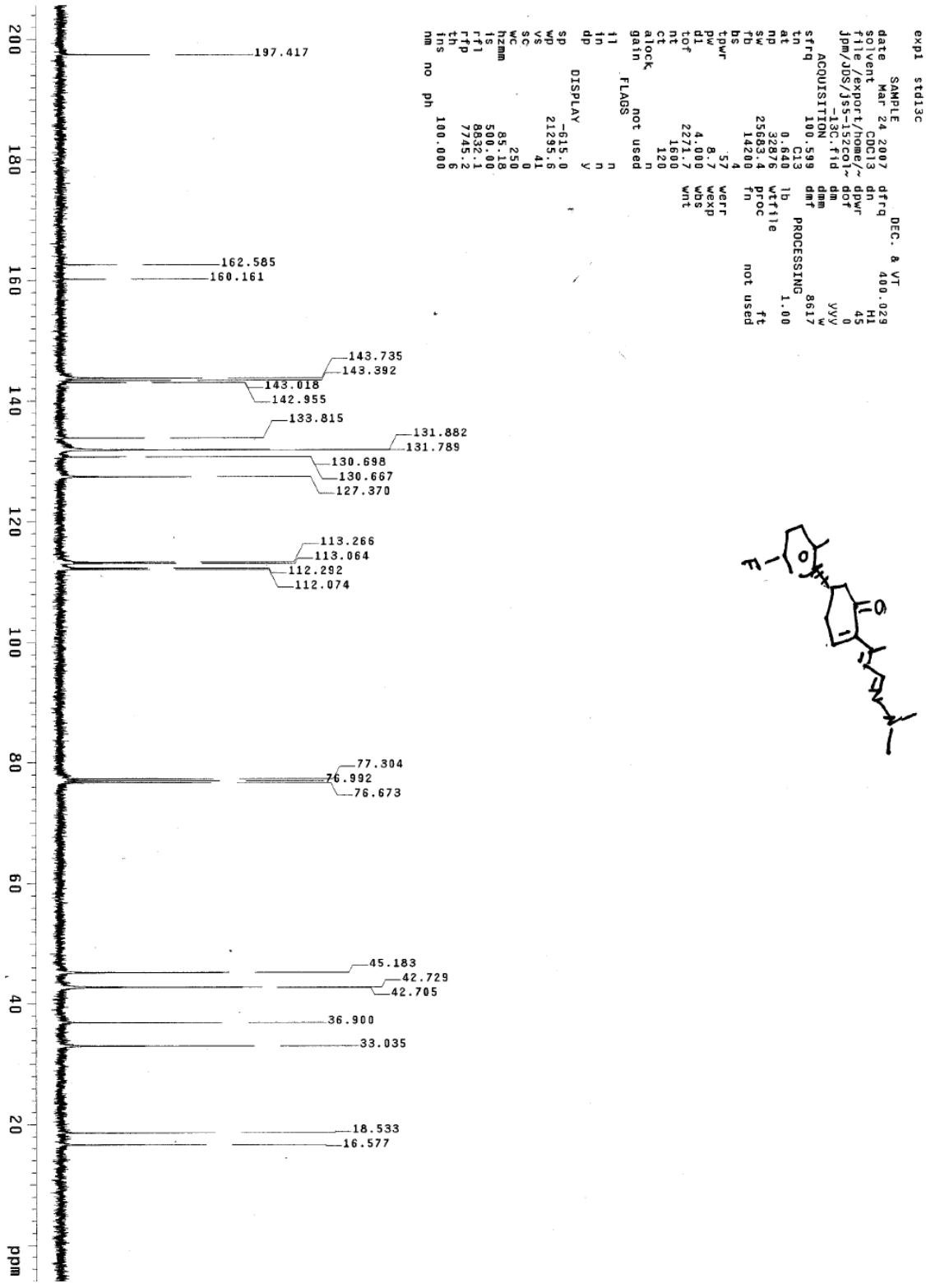
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76.673
45.183
42.729
42.705
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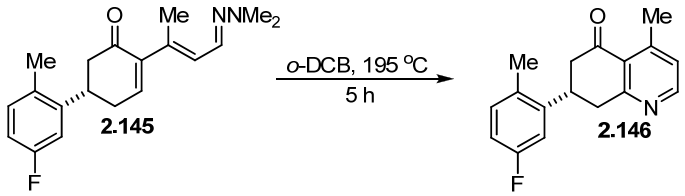
20
ppm

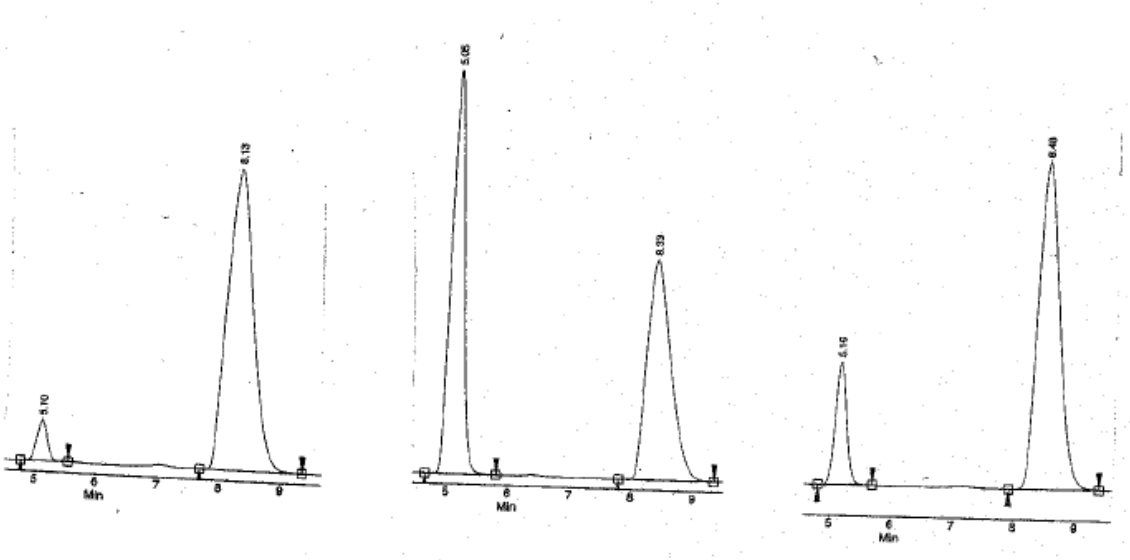
Synthesis of 2.146



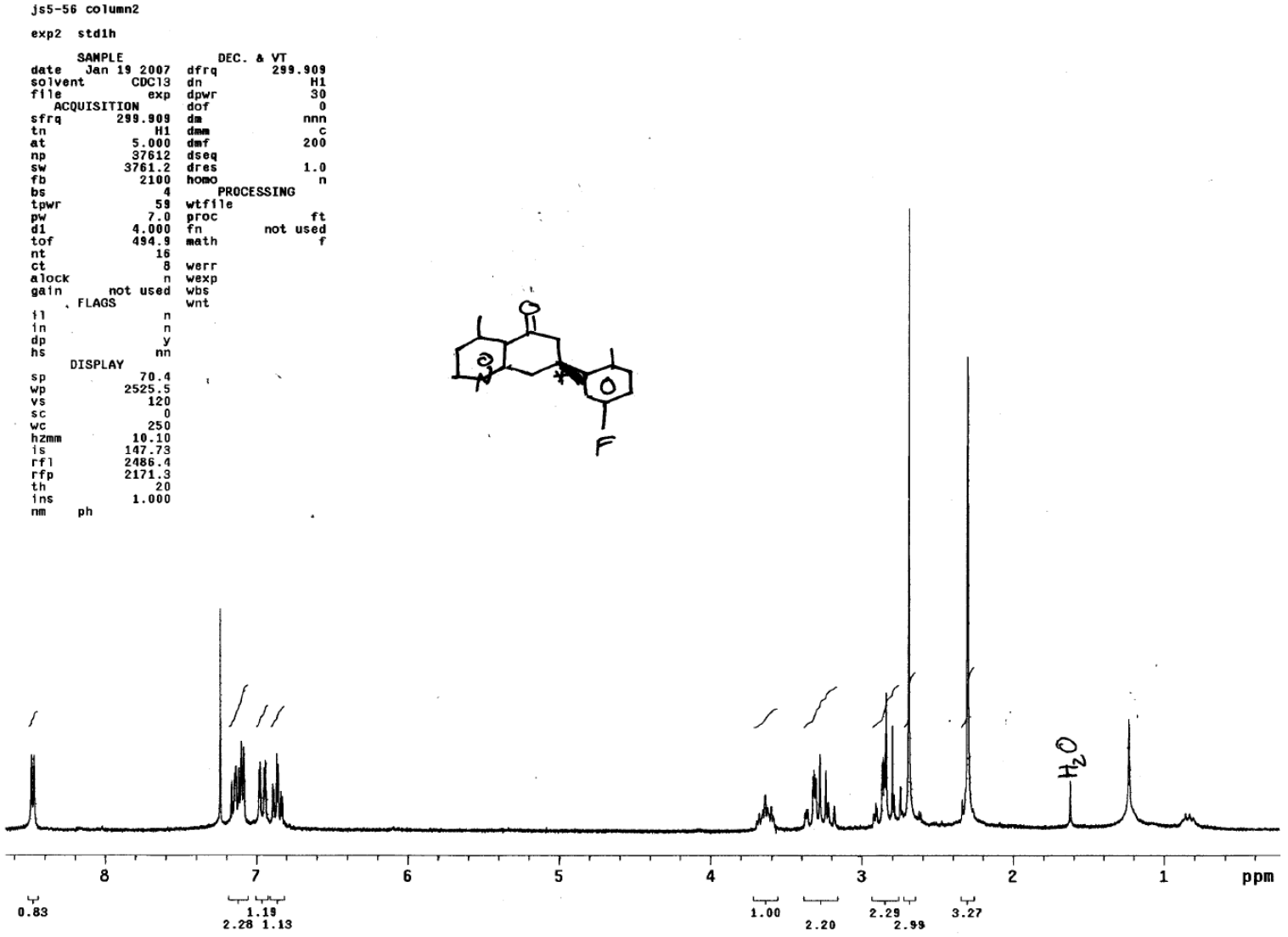
A solution of 24.8 mg (0.0789 mmol) of **2.145** in 1.5 mL of 1,2-dichlorobenzene (*o*-DCB) was heated at 195 °C for 5 h in a sealed tube. After cooling to room temperature, the solvent was removed under reduced pressure, and 9.0 mg (0.033 mmol, 42%) of **2.146** was isolated, as a white solid, after silica gel chromatography (one column in hexanes/EtOAc, followed by a second using CH_2Cl_2/EtOAc). Spectral data were consistent with the literature.[49] $[\alpha]_D^{20} = -4.8^o$ (c = 1.0, CCl_4). The enantiomeric purity of **2.146** was determined by comparison to authentic racemic material prepared by the known route.[1]

[1] Miki, S.; Suide, H.; Tawada, H.; Iwano, N.; Aoki, I.; Adachi, M. Process for the Production of Optically Active Cyclic Enaminone Derivatives. Eur. Patent 1,229,019 A1, July, 8, 2002.

*Chiral SFC (AD-H, Chiralpak, 150 bar, 50°C, flow = 5.0 mL/min, 5.0 % MeOH) analysis of **2.146**:*



2.146 | Racemic **2.146** | **2.146** + racemic coinjection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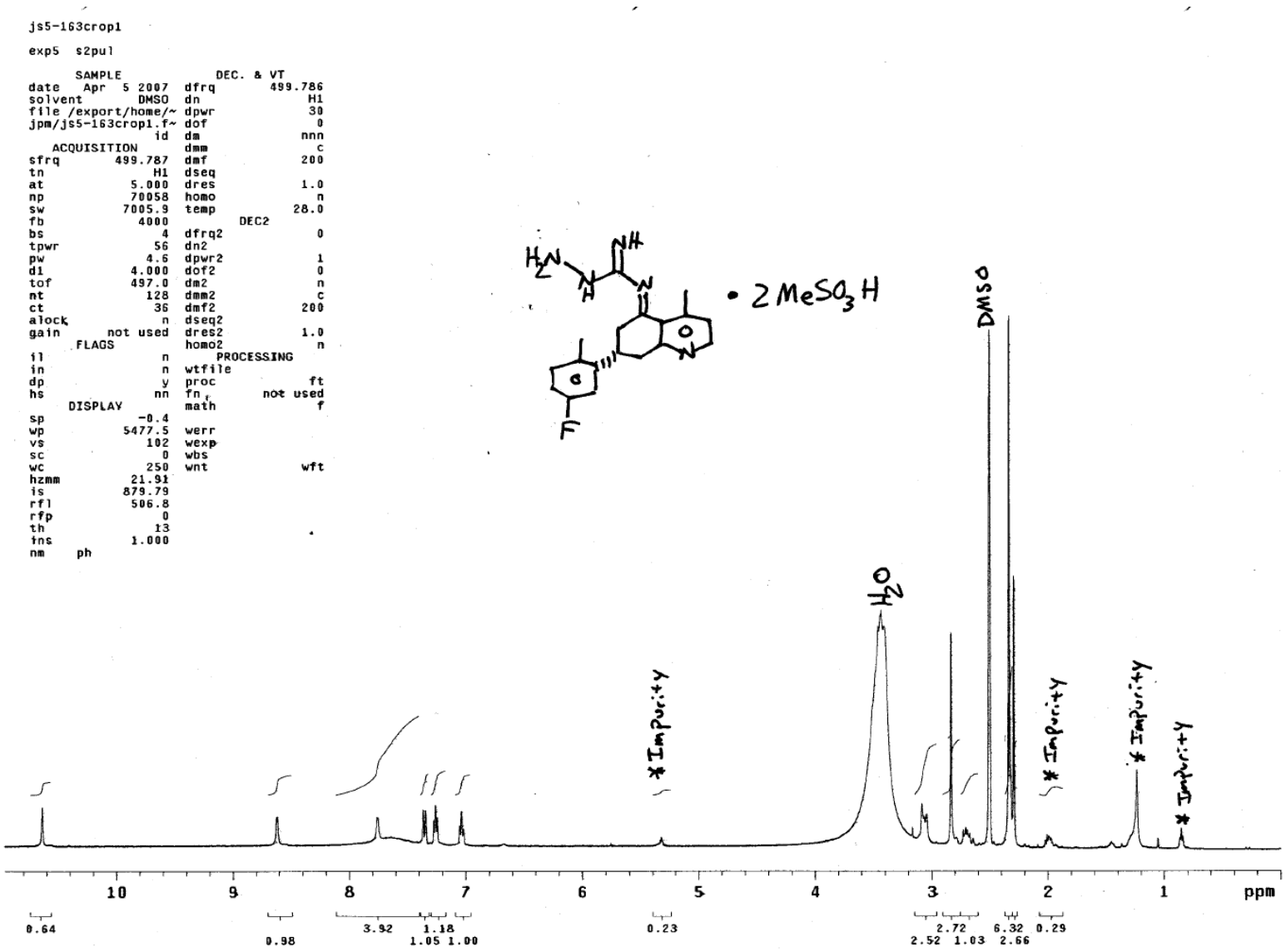
F
H2O
8
7
6
5
4
3
2
1
ppm
0.83
1.19
2.28 1.13
1.00
2.20
2.29
2.99
3.27

Synthesis of 2.148

To 8.8 mg (0.033 mmol) of **2.146**, in a 0.5 dram vial, was added 4.5 mg (0.041 mmol) of aminoguanidine·HCl, followed by 0.10 mL of anhydrous MeOH. The vial was capped, sealed with electrical tape, and heated at 65 ^{o}C for 30 min. After cooling to room temperature, 10 μL of concentrated HCl was added, and the vial was heated at 100 ^{o}C for 2.5 h. Volatile material was next removed under reduced pressure, after cooling to room temperature. The residue was diluted with 0.25 mL of anhydrous MeOH, and 35.7 mg (0.66 mmol) of NaOMe was then added. This mixture was allowed to stir for 20 min, and water was then added, followed by extraction with EtOAc (10x). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. This gave 13.2 mg of material, which was diluted with 0.1 mL of EtOH and 6.6 mg (4.5 μl, 0.069 mmol) of $MeSO_3H$ was subsequently added. Upon standing overnight in the freezer, a solid precipitate formed that was subsequently collected by filtration. The solid was washed with EtOH that had been cooled to -78 ^{o}C (dry ice/acetone) followed by Et_2O that had been cooled to -78 ^{o}C (dry ice/acetone). The solid was finally collected by rinsing the material through the filter funnel using MeOH, followed by removal of volatile material under reduced pressure. This afforded 2.0 mg (0.0040 mmol, 12%) of slightly impure **2.148**. Its structure was verified by comparison of the ^{1}H

NMR spectrum with the reported literature data.[49] Further purification by crystallization or chromatography on alumina was unsuccessful.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* Impurity
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6
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2.72
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0.29
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